Infection Control Devices Branch
Division of Dental, Infection Control and General Hospital Devices
Office of Dental Evaluation
Center for Devices and Radiological Health

32nd General Hospital
Panel Meeting

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Timothy Sullivan, MD -- Emory Clinic
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Industry Guest Speakers

Thomas Tillotson -- HIMA
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Professional Groups

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AORN representative present

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O P E N P U B L I C M E E T I N G (10:35 a.m.)

MS. O'LONE: Good morning, and welcome to the General Hospital and Personal Use Devices Panel Meeting. My name is Martha O'Lone and I am the Acting Executive Secretary for the General Hospital and Personal Use Devices Panel.

I would like to welcome everyone today to the panel meeting, and if you have not signed in outside the door, please do so right there at the sign-in desk. Also at the sign-in desk you will find copies of the agenda and information on obtaining a transcript, if you desire.

The next item of business is an item of business. I have to read a statement to the record on conflict of interest. For the General Hospital and Personal Use Devices Panel Meeting September 15th and 16th, 1997, the following announcement addresses conflict of interest issues associated with this meeting, and is made a part of the record to preclude even the appearance of any impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by the panel participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their, or their

employer's, financial interests; however, the Agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the government.

Limited waivers have been granted to all participants for their employment, or for financial interest in firms which could potentially be affected by the panel's decision. These include Dr. Jacqueline Simmons, Charles Edmiston, Elaine Hymek, Brahm Goldstein, who is not here today, Dr. Fred Whitehouse, Joseph Fowler and Ms. Christine Chandler and Ms. Marcia Ryder.

Copies of these waivers may be obtained from the Agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

Drs. Wava Truscott and Jay Slater are guest speakers with us today. Those speakers have acknowledged employment or financial interest with the firm whose product will be discussed today. With respect to all other participants, we ask in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose product they may wish to comment upon. Thanks.

And as I said, I am Martha O'Lone and I am Acting Executive Secretary for the General Hospital and Personal Use Devices Panel, and welcome again. I would like to introduce our Chair, Dr. Jacqueline Simmons, and then I will have the other panel members briefly introduce themselves.

DR. SIMMONS: Good morning. I am Dr. Jacqueline Simmons and I am Adjunct Assistant Professor Department of Epidemiology at the University of Miami, and a general internist from the University of Miami. And we will start from my left and go back to my right and have everyone else introduce themselves to you.

DR. FOWLER: My name is Dr. Joe Fowler, I am a dermatologist in private practice and Associate Clinical Professor at the University of Louisville, and current President of the American Contact Dermatitis Society.

DR. WHITEHOUSE: The name is Fred Whitehouse, I am an endocrinologist at the Henry Ford Medical Group in Detroit, Michigan, and Division Head Emeritus in the Division of Endocrinology and Metabolism at that institution.

DR. HYLEK: I am Elaine Hylek, an internist practicing at Massachusetts General Hospital in Boston, an Instructor of Medicine at Harvard Medical School, and a

member of our Division of Clinical Epidemiology at MGH.

DR. EDMISTON: My name is Charles Edmiston, I am a microbiologist, Associate Professor of Surgery at the Medical College of Wisconsin in Milwaukee.

DR. BOUWSMA: Otis Bouwsma, I am a periodontist. Currently I work for BIORA, Incorporated in Chicago, Illinois.

MS. CHANDLER: Christine Chandler, Nurse Practitioner, Clinical Instructor at Harbor-UCLA Medical Center in Los Angeles and an HIV Clinician.

MS. RYDER: I am Marcia Ryder, I am a nursing consultant in vascular access and also a doctoral student at the University of California San Francisco, Department of Physiological Nursing.

DR. SIMMONS: This morning, we as panel members were asked to make a recommendations to the FDA regarding a draft guidance document testing for skin sensitization to chemicals and latex products. We will now begin the open public hearing of this meeting today.

As you see from your agenda, we have two speakers. Before we ask the speakers to come up, we will also ask Dr. Lin, who is Branch Chief of Infection Control Division, to give us a little bit of an introduction. But first, I am

going to ask the speakers to please speak into the microphone, because we need you to be clear for our transcription purposes. We are going to also ask you to state your name clearly, your affiliation, and also, if you have any financial interest with the product at hand today. Dr. Lin.

DR. LIN: Thank you, Dr. Simmons. And good morning. My name is Chiu Lin. As Dr. Simmons mentioned, I am the Branch Chief for the Infection Control Devices Branch in the Division of Dental, Infection Control and General Hospital Devices in the Office of Devices Evaluation CDRH/FDA.

On behalf of the CDRH/FDA, I would like to welcome all of you coming to this and participating in the 32nd General Hospital and Personal Use Devices Panel Meeting today. As Dr. Simmons mentioned, the purpose of this meeting is to solicit your advice and input on the proposed draft guidance document that deals with the labeling claim of reduced chemical sensitization potential of a latex medical device.

I want to emphasize here that today we are talking about chemical sensitization, not protein-induced sensitization or allergic reaction, so we only limit it to

chemical. As we all know, the latex allergy has become a growing public health issue and to provide an improved latex product with a low sensitization potential is an important mission to the FDA, so this guidance document which will provide recommendations to manufacturers of latex medical devices on how to test their products and generate appropriate scientific data to support any claim that they may be interested to be on their product is one way the FDA utilizes to ensure the product can be used by any user with confidence.

With that in mind, we at FDA would like very much this guidance document as scientifically sound as possible, and therefore your input on this draft guidance document is going to be very important to us. This is why we commenced these panel meetings today, so we are looking forward to your expert advice and hope to have a very productive scientific meeting today. Thank you.

DR. SIMMONS: Thank you, Dr. Lin. We will ask our first speaker to come to the podium, Ms. Roberta Carlin, Associate Director, Spina Bifida Association. We are going to ask you again to please state your association -- your name, of course -- and if you have any financial interest with the product at hand.

MS. CARLIN: Yes, my name is Roberta Carlin, I am the Associate Executive Director at Spina Bifida Association of America, and I have no financial interest.

DR. SIMMONS: Thank you.

MS. CARLIN: I am here on behalf of SBAA. We are a consumer group. We are the large national association that deals with persons with spina bifida, our primary mission is to prevent spina bifida and to enhance the lives of all those that are affected.

I am here specifically to address the latex issues. We are not presenting any scientific testimony. I am here on behalf, as I said, of the consumer group. I realize that the focus of your conversation and decisions today deal with Type I allergies, or rather Type IV allergies; most of the situations that the spina bifida person is involved in are the Type I allergies. However we feel that it is important that everybody is aware of the critical and life-threatening problems faced by those with spina bifida and latex allergies.

As I said, I realize that my comments and video encompass more than the specific aspect of your discussions today, but I brought a very brief, five-minute video which I hope you will enjoy, and I guess I must also add that one of

our major concerns is from reading the claims and the testing devices regarding these new products, is that the claims are very clearly written to make sure that the general public and those with latex sensitivity are not confused, and I think that is a real issue. I will answer any questions afterward.

[Video omitted from record.]

DR. SIMMONS: Do you have any questions -- for the speaker?

DR. WHITEHOUSE: The 40% figure that was mentioned in the show, how was that garnered? Was that a prospective study, does it include irritants Type IV and Type I, or -- could you comment on that a little bit?

MS. CARLIN: I do not know the answer. I can certainly get back to you on that, but I do not know the answer. I know that the numbers vary. We have some information that we put out that cites the incidence between 17 and 83%, but --

DR. SIMMONS: Any other questions? Thank you.

MS. CARLIN: Okay. Thank you all. As I said, I realize that this presentation is much further in scope than what you are specifically dealing with, but medical devices with latex are certainly a critical issue to persons with

spina bifida and the labeling claims have to be very well-written and very user friendly. Thank you.

DR. SIMMONS: Thank you. We will ask Dr. Shapiro, Lee Shapiro, to come to the podium, please? And before you speak, could you state your name, your affiliation, and if you have any financial interests in the product at hand.

DR. SHAPIRO: Good morning. My name is Lee R. Shapiro. Until recently, I was a practicing dentist in private practice. I have no financial interest in the outcome of this meeting.

I have been practicing dentistry for 20 years. I started wearing latex gloves approximately in 1982 with no problems at all for, I would say, a couple of years. As I get older, the years kind of blend together and I cannot really pinpoint exactly when I noticed my first problems.

It started out -- the reaction started out as a mild, what I would call, annoying reaction; basically, itching and redness on the backs of my hands, and eventually what I did was I just switched to a different brand of gloves and that seemed to help for a time, but then the problem reoccurred, and again, I switched to a different brand and I basically put up with this for several years and it was not so bad that I could not work. It was more of an

annoyance, as I said before.

It was only in the last perhaps year that my condition has gotten a lot worse. My problem led me to seek the services of a dermatologist. At that point my hands were constantly red, with tiny bumps on the backs of my hands. The biggest problem was the intolerable itching, and it might seem minor, but the itching became tortuous, to the point where I felt like I could not stand having the gloves on any longer and I would hurry through procedures and I could not wait to get the gloves off and wash my hands in cold water.

My dermatologist thought when he first looked at it that this was something that he could clear up. He put me on a potent cortisone, topical cortisone, and that did get rid of the problem, and his plan was to gradually reduce the potency of the cortisone by using different products, and then eventually get me off the cortisone completely because it is not something that you can use indefinitely. And it worked as long as I was using some type of cortisone, but then shortly after I would stop, the problem would return, and then we went through the procedure again, with the same results, and finally, I heard about another dermatologist who was doing allergy testing and I decided

that I should consult with him and I had a series of 80 different patches placed on my back for different chemicals that are found in the dental office, and the two that I reacted positively to were the carbamates and the thiurams. At that time, I had no idea what these chemicals were, but I quickly found out that they are components used in the manufacturing of latex gloves.

I went back to my primary dermatologist with those results and he really had no alternatives to offer me, and he basically asked me if I had a good disability policy, which I said, I did. The bottom line is that it was so bad that I decided to look into the possibility of going out on disability and selling my practice and finding something else to do, which actually about a month ago, I did just that. I sold my practice, my disability is still under review by my insurance company. I do not know if they are going to approve that yet.

I tried using vinyl gloves and that did result in an improvement, but did not totally resolve the problem, and I also had concerns about using the vinyl gloves. I did not feel that they provided the same protection as latex gloves as far as barrier protection and also they would tear easily, and I just did not feel that they were a safe

alternative, besides the fact that they did not fit well and made it difficult to do my procedures.

I also tried cotton liners under the latex gloves and that actually made the problem worse, and I feel that is because it trapped heat and perspiration against my skin and apparently the chemicals were still getting in there anyway and that just made the problem much worse. So, after trying various liners and nonsteroid creams to put on my hands and nothing worked, so the decision was finally made to just give it up.

Also, my concern at that time was, I realized that what I had was a Type IV allergy and that it was not health-threatening, it was quality of life-threatening, but my concern was that it could develop into a Type I allergy and I just was not willing to take the chance and continue in practice under those conditions.

That is basically my experience. Are there any questions?

DR. SIMMONS: Any questions from the panel?

DR. SHAPIRO: I might add that my daughter who is 19 years old who is in college and works in the biology lab, she has experienced some problems, also, and I am concerned for the well-being of my children. This particular daughter

wants to go into research. I have another daughter who wants to go to medical school, and I do not want the same thing to happen to them; I want them to be able to pursue the profession that they want, and I hope that that will be the case.

DR. WHITEHOUSE: Do you have other allergies?

DR. SHAPIRO: I have hay fever type allergies, have since I was a child, to pollen, dust, mold, and so forth. I have never had a drug or a food allergy that I know of, but I am an allergic type person, as are my children.

DR. SIMMONS: Thank you.

DR. SHAPIRO: Thank you.

DR. SIMMONS: Is there anyone else in the room who would like to speak at this time in open hearing? Open public meeting. Thank you. I guess we can go on now to the next portion of the meeting and we will start with Dr. Lin again.

Dr. Lin will give us a historical background on the latex guidance.

Agenda Item FDA Presentation of Guidance Document:

DR. LIN: Thank you, Dr. Simmons, again. I thought my role here today is to give you some kind of a

perspective, historical perspective, on how we got to here today, and how we developed -- what the reasons, how we developed this guidance document to help to improve the product.

As we know, the latex sensitivity or latex allergy, this phenomenon is not new. I think that 'way back in the early nineties there were already people already know all those phenomena. However, all those that the issue, the problem, started within about the mid-eighties, 1980s, with the discovery of AIDS and then the CDC's universal precaution, recommendation, and then healthcare workers started to increase the use of latex devices, particularly the medical glove, to protect from AIDS or other infections, and because of this, the latex issue has become increasingly -- become a public health issue.

This problem was highlighted in about May 1990, the Agency started to receive the reports of tests, but in May 1990, I think that that is the highlight of all of these issues.

This is the basis that mostly results from this spina bifida patient that is exposed to the latex tip of this barium enema kit, and also, this is the problem, also exacerbated, when in 1991, in December 1991, OSHA published

this problem pathogen kit, which required that all the healthcare workers had to use the medical gloves and other protective devices, and that also exacerbates the latex allergic reactions. As I said, this problem has become a public health problem.

We are already -- probably all of you are aware of that there are at least three types of reactions to the rubber latex. The first one is the so-called irritation contact dermatitis. Most of it as far as we know, is caused by residual processing chemical additives.

The second type reaction is what we call the Type IV reaction, or Type IV allergy, also delayed type hypersensitivity. Again, this is also caused by residual processing chemical additives.

And then the third type of reaction is Type I allergic reaction, also, is immediate type hypersensitivity, and this, as far as we know, is caused primarily by latex proteins contained in the latex rubber.

When we talk about problems, as far as the FDA is concerned, the problem comes with at least three dimensions. The first dimension is that some fraction of a population may be allergic to the latex product, but may not be aware of their allergies. That is just one of the situations.

Then the second situation, as I mentioned, there are at least two types of immunological reactions that can occur to a latex product; so you have a chemical sensitivity, or you have a protein-induced Type I reaction. And furthermore, as far as the FDA is aware, some manufacturers may not be using state-of-the-art technology for manufacturing latex medical devices, which leaves very high concentrations of undesirable latex origin on the product. And so, because of all these situations, the FDA -- since as mentioned in the early nineties, FDA started to initiate several activities to try to address this issue.

The first one on my list here, in March 1991, FDA issued a medical alert, tried to alert the medical profession of these problems. And also, in November 1992, FDA also sponsored an international latex conference, tried to find out what is our overall prevalence or incidence of all of the latex sensitivity issues, problems.

Also in March 1994, FDA also convened a scientific workshop, and this workshop strictly talked about the contact dermatitis issue caused by chemical residues and as a result of this workshop, we drafted this guidance document and that is the main subject of these panel discussions.

Also, in May 1995, in order to encourage to

improve a product, tried to reduce the protein content of latex products. We realized by now -- we do not know much about the protein nature inducing this is Type I reaction, but at least, as far as the FDA can do, is to encourage the manufacturer to produce a low protein medical device, particularly, medical gloves. So, we have produced a guidance document, tried to advise the manufacturer on how to proceed to make this a low protein product.

In June 1996, we also published a proposed Federal Register rule to require -- and the purpose of this rule, essentially is to require all the latex-containing products to be labeled as to the latex contained in their label, and also, in July 1997, FDA also released this proposed guidance document, Testing for Skin Sensitization to Chemicals in Latex Products. On the FDA Internet, we solicited comments and again, this is our main subject for discussion today.

Here we are in September 1997, we are discussing this guidance document so we are grateful for all of you to come in to this panel meeting and provide the input to the Agency.

As I mentioned, in June 1996 we published a proposed rule. Essentially, the rule has two proposals; one is that they require natural rubber latex containing medical

devices be labeled with a statement such as, this product contains natural rubber latex, which may cause an allergic reaction in some individuals.

Or this product has a component that contains natural rubber latex which may cause allergic reactions in some individuals. Or, they can provide such a statement as, this product is made from natural rubber latex which may cause an allergic reaction in some individuals. So, whoever is sensitive to the latex, there will be a warning that they are dealing with some latex product.

And then the second proposal is that the FDA is going to prohibit the labeling claim of hypoallergenic claim on some natural rubber latex gloves or some other latex-containing medical device, and in return, the Agency is planning to allow for labeling claim regarding that sensitizing potential of the residual manufactured chemical additives.

As mentioned, for the research proposal, FDA is going to propose to prohibit the use of that hypoallergenic term. Starting in 1989, when some manufacturers came to the FDA and requested to label their product as hypoallergenic, and at the time FDA thought, well, in order to support a hypoallergenic test, FDA recommended that a negative result

from a Modified human Draize test conducted on 200 human volunteers. If you can show that your product passes these two tests, at least 200 human subject test, then that product can be labeled as hypoallergenic.

After several years of this product on the market, FDA discovered some problems. The first, and the FDA received many, many reports of sensitivity to this medical glove, particularly, labeled as hypoallergenic. And we also found out, a I mentioned, you have two types of reactions, and so when you talk about hypoallergenic, you are talking about chemically-induced hypersensitivity or your protein-induced hypersensitivity, so that is the problem.

Right now, as probably we all are aware that the Modified Draize test essentially is designed to detect the contact dermatitis, the Type IV reaction, not designed for detecting protein-induced Type I reactions. So, what exactly does hypoallergenic really mean to the user. This has become a very misleading and misbranding labeling claims. So, that is the reason that the Agency tried to prohibit the use of that term.

I mentioned before, in order to encourage the manufacturer to produce a low protein medical device, particularly medical gloves, we have in 1995, May 1995, we

also issued a guidance document dealing with the protein content labeling.

Essentially, this protein content labeling that if the manufacturer, by using the ASTM standard test method taken for measuring the protein content of the water insoluble proteins, then they can label their product such as, this latex glove contains X-amount of a microgram or less of total water insoluble protein per gram of medical glove and this is the best at the time the Agency can do to encourage the manufacturer to produce a medical glove which contains a very low amount of protein. But again, for that, that reduction of a protein content transpires to reduction in allergic reactions or not, we do not know. So therefore, we also ask the manufacturer to put their caution statement, the safe use of this glove by non-latex-sensitive individuals has not been established. So, until we have a more scientific data, then we may change this requirement.

Again, so in July of 1997, we also finalized a proposed draft guidance document dealing with the chemical sensitization. So this is where we are today, so that will give you an historical perspective of how the Agency comes today, so we commend this panel meeting. Again, I want to thank you, everyone.

DR. SIMMONS: Thank you. We will continue our FDA presentations, and our next speaker will be Dr. Vesna Tomazic-Jezic. Office of Science and Technology. She is an immunologist and she has been with the FDA working on latex issues for about seven years. Thank you.

DR. TOMAZIC-JEZIC: This document that I will be presenting today has been in development for a number of years; actually, ever since we had that workshop with the same title organized here at the Agency in 1994.

Based on recommendations of the panelists, which included some dermatologists and some allergists and representatives from industry, we prepared the first draft and that first draft was then circulated among the panelists themselves and other clinicians that were in the same area of expertise. Also, among the number of industry representatives, and also among the colleagues here at the Agency. And was certainly revised several times due to many comments that we received.

This particular version that we have now includes more or less all the suggestions that we have been receiving to that period of time. And in spite of the responses from different people, we still would welcome any additional comments and suggestions from the panel and from the

audience.

I just want to reiterate what Dr. Lin said before. Adverse reactions to latex includes three different types, and irritation is one which is nonimmune, basically direct injury to tissue exposed to latex chemicals. The second one is Type IV allergy which is immune response, also to latex chemicals and the Type I which is immune response to latex proteins. All three of them certainly present a problem and they are all addressed by the Agency in a different manner; however, I just want to stress that today we talk again only about Type IV allergies, and the document here is only addressing that particular issue.

Type IV allergy is cell-mediated immune response and appears usually about 48 hours after the exposure and it is therefore addressed as delay-type hypersensitivity also. It is caused by residual manufacturing chemicals on the finished latex product, and symptoms of the Type IV reaction in this case is actually limited to the skin reaction, defined as allergic contact dermatitis.

It is mainly limited to the area of exposure, although it can spread somewhat and occasionally appears on a distant site, but not very frequently. As we all know, this is not a life-threatening condition but it is still a

very serious health impacter on the individuals, and one reason is that it occurs in a high number with frequent users of latex products, actually especially those that are exposed occupationally. And also another problem is that symptoms of contact dermatitis, when they appear, they last for several days, and therefore if you have a frequent use of latex gloves, basically it turns into a chronic problem.

As you just heard from Dr. Lin, and I am sure that you all knew before, that hypoallergenic label existed on the market because manufacturers were long aware of this particular problem. They tried to develop products with a reduced level of chemicals, and labeled them hypoallergenic, and again, the label was only referring to Type IV allergy, and also the testing for the claim was only for Type IV allergy. So, now as we all know, that Type I is so prominent a problem in the public today, that that became a quite confusing and misleading label, and I guess it is not illogical to assume that many of the users may not be very aware of what is the difference between Type I and Type IV, and therefore when they see hypoallergenic, they assume this is safe for their own use.

The purpose of this particular document is to allow manufacturers to continue producing and marketing this

improved product and actually even better, developing an new better product, and therefore we developed this document that will indicate our options for a new label that would clearly define that it is related to chemical sensitivity.

So basically, what this document is proposing is two different claims and one that is intended for individuals who are not sensitized and can use a product that will not sensitize them or develop induced Type IV allergy, actually, that one would benefit almost all the users of latex gloves.

The second claim would actually specify that a product can be used even by those who are already sensitized. So, the main point in today's discussion will be basically a description of these two claims and then discussion about the recommended testing for each of the claims.

This is a full text of the claim #1 as it is stated in the document, and it says that, it will not induce sensitization in healthy, nonsensitized individuals, and recommended testing for this particular claim would include a Modified Draize Test 95, and I will come back to that in the details.

I also want to point to the cautionary notice on

the end of the claim which says that, although it is safe for nonsensitized individuals, it has not been tested for safe use in those which already have allergy to the latex chemical.

This is the text of Claim Two that says, the product can be used by individuals who are already sensitized and would be stated as to which of the chemicals. There are, as we know from basically clinical studies, there are three major groups of chemicals that are used in the manufacturing of the latex gloves and they present major sensitizers. Those are thiurams, mercaptobenzothiazoles, or MBTs, and carbamates. So, it will be one or the other or the third or all three of them stated in the claim depending on the product.

Recommended testing for this particular claim would include, in addition to the Modified Draize-95 test, also a patch test on individuals who are already sensitized, who already have positively diagnosed allergic to one or more of those chemicals.

Back to what is Modified Draize test? The original Draize test was developed more than 50 years ago with the purpose to evaluate the potential of chemicals to induce Type IV or delayed type hypersensitivity in animals,

and it has been used since then for determining a variety of chemicals. In 1996, actually, it was adopted to use in humans for a similar purpose, and since then it was intensively used actually for evaluating cosmetic products for potential sensitization of chemicals in those products. Through this experience it appeared to be a pretty good predictive test of the potential for sensitization.

The Modified Draize-95 test is another adaptation, specifically for testing of latex chemicals. The changes and modifications are based again on the clinical experience from earlier studies as well as some scientific facts that appeared in the last number of years, and now I will describe in detail some of the procedures involved in the testing.

The basic testing procedure includes application of nine patches of the test article, size one square inch, and each patch is applied for 48 hours with full occlusion on the back of the test subject. After 48 hours, the patch is removed and replaced with a new one of the same article, and so on, until nine patches are completed.

For the convenience of the test subjects as well as the testing labs, we adapted the schedule of 48-48-72 hours, which actually means that individuals can come on

Monday, Wednesday, and Friday, and have the patches removed and replaced, and the one that is placed on Friday would stay until Monday, and until all nine patches are placed.

Also, I would like to say that our previous Draize test that was used for hypoallergenic claim earlier, was based on ten patches rather than nine, and we reduced that again for the convenience of test panel subjects as well as testing labs, so that all testing can be completed in three weeks, period.

After that, test subjects are rested for two weeks without any additional patching, and then they are called in for a challenge patch, and they are actually receiving two patches, one the same size as the induction patches. One is placed on the same site where induction patches were placed, and another one on the virgin side. And readings of the reaction performed two days after application, which is at the time of removal of the patch, and then four to six days after the application.

Criteria for the selection of the test subjects were also based on clinical experience as well as recent published data, and it is recommended that the panel consists of 300 nonsensitized, healthy human volunteers, ranging in age from 18 to 65, which actually includes the

entire working age of the individuals, basically the age when the occupational exposure really occurs.

In order to ensure predictability of the tests, the composition of the tests panel should as much as possible reflect the user population, and therefore consideration should be taken for proper racial and gender diversity of the subject panel.

Exclusions as stated in our document include all individuals with any visible skin disorders that may interfere with the reading of the results of the test. Also those individuals who already have a Type IV allergy should be excluded; and also, individuals that have a Type I allergy to latex proteins, and this is only in order to avoid any undesirable adverse reaction during the testing, however that does not mean that all atopic individuals should be excluded. Quite contrary, that should also be taken into consideration because some literature data indicates there is a correlation, the others do not, so I think it is safe to include both of them. Also, individuals who are using corticosteroids, either systemically or topically at the potential site of testing should be excluded and of course, pregnant women should be excluded.

Testing should be performed on two environmentally

different locations, in order to account for the possible effect of temperature and humidity on the skin condition and certainly consequently on the response to the test articles. Scoring of the reactions can be performed based on recent ASTM Provisional Standard 7797, and for passing it is recommended that all 300 individuals present a negative reading and the negative reading would be any reactions of less than 1+, scored according to ASTM standard.

Irritation of course would not be acceptable, and therefore when a challenge patch is applied, caution has to be paid to distinguishing irritation versus sensitization. These two reactions are frequently hard to distinguish in terms of skin symptoms, however a better marker to distinguish these two reactions would be the time of appearance and duration of the reaction. As I said, irritation usually appears shortly after the exposure and actually is eliminated more or less after elimination of the source of the problem, while allergic contact dermatitis would appear two days after exposure and then would last for several days, so that could be kind of an easier way of distinguishing these two reactions.

Regardless of very cautious evaluation of test subjects and questioning them before including them into the

panel, we assume that there may be some of the individuals that are presensitized and would be identified during the test procedure. Namely if positive reaction occurs after one or two patches, such individuals should be considered presensitized, and in such cases they should be taken out of the 300 panel study and no other patches should be applied, and then two weeks later they should be challenged like any other later members of the test panel to confirm presensitization or distinguished from irritation.

For Claim Number Two, in addition to this modified Draize test that I just described, it is recommended to perform testing on 25 individuals with confirmed allergy to particular chemical sensitizer that the manufacturer intends to state in the claim.

For both this group as well as for 300 samples in the Draize test, statistical evaluation and logistics for selection of sample size will be discussed by Dr. Kaczmarek after me. The testing of these individuals will include the single patch, again, one square inch in size, similar to the challenge patch in the other test. The patch will be placed for 48 hours with complete occlusion, and the readings will be performed at the time of renewal, which is two days after the application, and the second reading, four to six days

after the application.

To qualify for the claim, it is expected that all 25 allergic subjects would be presenting readings less than 1+. Another thing, when talking about a positive diagnosis of allergy in those individuals, we are referring to a minimum of 1+, according to North American Contact Dermatitis Group Standard.

We are aware that individuals can be highly sensitized and less sensitized, and most likely those highly sensitized would respond much stronger, or to a lower dose than the less sensitized individuals, however the document does not specify the level of sensitivity for those 25 individuals, and this is one thing where we would appreciate input from the panel of what would be the optimum for this.

This is just to summarize what I just presented. There will be -- this document proposes two options for labeling products with lower chemical sensitizer level. And the first one would really benefit the majority of the users of gloves, and ensure them that even if they are using them on a frequent basis, they will not become sensitized.

On the other side, the second claim, if manufacturers manage to produce such a high quality product, they could label and modify that, and benefit those who are

already sensitized to particular chemicals. This population is still a relatively limited one, so basically even a few of those products would be of enormous value for those individuals, and as we just heard this morning, individual professionals who have to use gloves in their profession have choices, either not to use them if possible, and use some kind of substitute, or basically change their occupation due to those persistent problems.

DR. SIMMONS: Thank you. We are going to move right on to -- and we will probably ask questions later, but we are going to move right on to Dr. Ronald Kaczmarek, who is a Medical Epidemiologist at the FDA, who will speak to us about statistical issues.

DR. KACZMAREK: I am Ron Kaczmarek, a Medical Officer and Epidemiologist with the Office of Surveillance and Biometrics of CDRH. I will discuss statistical considerations in the draft guidance document.

I would like to begin with a series of initial observations; first, increasing the sample size of the study increases the precision of a study; this is true even for large sample sizes. Secondly, increasing the sample size of a study increases the cost of the study; this applies both as a general rule and in this particular instance.

For example, if the sample size of the nonsensitized group is increased, there will be increased costs for both study participant recruitment, and testing. The optimal sample size is a tradeoff of both precision and cost.

This slide describes the study's objective. A negative study should be incompatible with the ability of the device in question to sensitize a substantial proportion of exposed individuals. Selecting an upper confidence limit of 1% fulfills this objective, for if all negative results are obtained, and the upper confidence limit is 1%, there is strong reason to believe that the sensitization potential of the device studied is less than 1%.

This slide describes the sample size calculation process that we performed for the nonsensitized group. We began by employing a very high level of confidence in the results, a 99% confidence level. We selected 1% as the upper limit of this confidence interval. Sample size calculations demonstrated that 450 study participants would be required.

We continued our sample size determinations with the observation that a 95% level of confidence is both widely accepted and widely employed in medical studies.

Employing the 95% level of confidence for the nonsensitized group reduces the required sample size to 300 study participants. This is a substantial sample size reduction of one-third, or 150 individuals. Most importantly, adequate confidence in the results is maintained; 300 study participants is the sample size we selected for the nonsensitized group.

This slide describes special considerations in the sample size determination for the group of known sensitized individuals. There are a number of potential difficulties in performing the study. First, there may be difficulty in locating sensitized individuals. Many individuals may be simply unaware of their specific chemical sensitivity. Second, there may be substantial difficulties in recruiting sensitized individuals. Not surprisingly, known sensitized individuals may refuse to participate in the study.

Third, there may be potential health risks from testing known sensitized individuals. This is an issue that we particularly seek the panel's view of, whether the potential health risks are clearly outweighed by the benefits of testing known sensitized individuals.

Due to the potential difficulties just described, the sample size for the group of known sensitized

individuals should be determined on a clinical, as opposed to statistical, basis.

FDA sought the input of clinicians to address the sample size issue for the known sensitized group. They indicated that a sample size of 25 would be appropriate. If all negative results were obtained, the upper limit of the 95% confidence interval would be less than 11.3%.

In conclusion, a sample size of 300 is warranted for the nonsensitized group. Second, the sample size of the test group of known sensitized individuals must be determined on a clinical basis. Thank you.

DR. SIMMONS: Thank you. I am going to ask the panel members if they have any questions for the three previous speakers? Any panel members, any questions? If not -- okay. Dr. Bouwsma.

DR. BOUWSMA: Since I am new to this, I have several that I could ask.

DR. SIMMONS: Okay.

DR. BOUWSMA: Why were pregnant women excluded from the -- I thought that this was a trend within FDA that we were trying to take all comers in clinical studies, including women that were pregnant, so my question is, why were they excluded?

DR. TOMAZIC-JEZIC: Well, there was a suggestion by some dermatologists that I discussed that issue with, that there are many conditions in which immune response is compromised, not maybe severely compromised, but is changed from the normal immune response, and pregnancy as well as women who are breast-feeding are indicated to be excluded, and there are other things that we got suggestions subsequently to the final version of the document, and basically we did not state that any other immuno-suppressant should be taken into consideration and they will be probably be added later in the final version.

DR. BOUWSMA: I guess -- you know, I certainly do not want to make a rule one way or the other, but if there are sensitization issues within women that are pregnant, isn't that something that we should know?

DR. TOMAZIC-JEZIC: Possibly, but basically this test is meant to be more or less a standard evaluation of a certain dose, and if you have a variation in the immune response of those individuals, then I guess we are divergent from the standard, and if they are more sensitive or less sensitive, that will implicate whatever standard results we receive from the test panel. Was I clear on that? I mean, if they are more sensitive, compared to the results of the

test and say, okay, this is more risk for me now than usually or the other way around. But the standard results should be obtained with a uniform population of optimal immune response.

DR. SIMMONS: The second question?

DR. BOUWSMA: The Type I versus Type IV, the numbers and percentages of people that are likely to be involved in these responses within the general population. Can someone tell me about that?

DR. KACZMAREK: Yes, I will certainly address the Type I issue, that is an issue that we are actually actively studying. As you are aware, healthcare workers are recognized as a high risk group for latex allergy that is Type I, and in fact, we published a study that found 5.5% of them on a nationwide study had evidence of latex-specific IGE antibodies. Overall, the precise percentage or proportion of healthcare workers known to be allergic to latex is not known. There is a range between 5.5%, or as high as 20%.

The general population has been estimated between 1% and 6%. The 6% number comes from a study by Dennis Omby of blood donors in southeastern Michigan. We at FDA currently have a study in the general population that is

currently underway, where we are looking at latex allergy on the basis of in vitro testing, and we expect to have those results ready by next year.

DR. BOUWSMA: Okay, and then -- I mean, I appreciate your -- it seemed like you were trying to help me out by reducing the numbers of people that had to participate in the clinical trials, and that is good, because it does mean less dollars expended for that, but if these numbers are correct, and there are a lot of people who are sensitive, why is that -- it seems like not a reasonable tradeoff to reduce the sample size; why not just keep it at the numbers that you had proposed originally?

DR. KACZMAREK: You mean, at 450?

DR. BOUWSMA: Well, basically, the 450 number is based on a 99% confidence interval, it is a very high level of confidence. What is standard in medical studies is 95%, that is what is customarily employed. It is widely accepted and it is widely utilized.

When we ran the numbers at 95%, we saw the sample size was reduced substantially; one-third, or 150 individuals; however, we are still maintaining adequate confidence. I would not support going below the 95% confidence level, but I feel very comfortable stating that

95% confidence is appropriate.

DR. BOUWSMA: Do these studies have to be done in the United States?

DR. KACZMAREK: I will let Dr. Tomazic address that one.

DR. TOMAZIC-JEZIC: Well, I think that is more a policy question and maybe Dr. Chiu Lin can answer this.

DR. LIN: As we stated in our guidance document, this is considered as kind of an ID study, although we consider as a nonsignificant risk device, however there is an investigational device regulations on that. So, as long as the test or the standard meets that kind of criterion, that any study whether it is conducted in the United States or in foreign countries, as long as the same criteria or scientific input or scientific strength can be reproduced, then all the data not necessarily has to be conducted in the United States.

DR. BOUWSMA: And all studies would be considered -- I mean, this is not where you do five or six studies and you get the right answer one time and then that satisfies anything? I mean, all studies are included within the data submission to the agency?

DR. LIN: We hardly see any people submit to us

five or six studies, but as part of the scientific review, if you have the multiple data, of course we would like to see the multiple data, whether it is positive or negative and we make a determination from that.

DR. BOUWSMA: Okay, thank you.

DR. SIMMONS: Thank you. I think we are going to adjourn the first portion of our open meeting and adjourn for lunch. We will ask you to be back at 1:30.

[Whereupon, at 12:00 p.m., a recess was taken until 1:30 p.m. that same day.]

A F T E R N O O N S E S S I O N [1:35 p.m.]

DR. SIMMONS: Good afternoon. We would like to begin.

We would like to begin our open committee discussion at this time. This last session should -- we are scheduled to continue until about 5:30. What we are going to do this afternoon is we have several scheduled speakers, who will assist the panel in giving us information about latex chemical sensitivity testing that should assist us in discussing the understanding, the key points in the guidance. I think we have six scheduled speakers and what we plan to do is to ask each speaker to speak no more than 15 to 20 minutes.

After that, when all the speakers have discussed their items, we will then have a panel discussion, wherein the panel will ask questions.

So, what we are going to do from 1:30 until about 2:30, we will have our speakers and then from 2:30 to about 3:00, we should have discussion.

I am going to ask the speakers to -- as they come up to speak, that they give us their names, their affiliation and also any financial interest they may have in any medical device company. The speakers are also invited to stay after their presentations so that we may ask questions during the question period.

So, at this time we would like to begin. And I think our first speaker -- and I am going to take them in order -- will be Dr. Jay Slater, who is an associate professor of pediatrics at G.W. University here in Washington. He is also an allergist and immunologist at Children's Hospital here in Washington, D.C.

DR. SLATER: Thank you very much.

Well, thank you. I really appreciate being invited. I will keep my remarks very brief because much of what I have said has been covered already. Actually, before I even start into the short substance of my talk, I would just like to cover what I think are some important clarifying points at this point.

We have gone back and forth between Type IV and Type I reactions and you have been told repeatedly that the focus of today's discussion is on Type IV reactions and, yet, there has been a lot of mention of Type I reactions,

which is, in fact, my area of expertise.

I want you to understand that there is a reason for this, that this isn't simply switching back and forth among different kinds of allergic reactions. There is some evidence that suggests that Type IV sensitivity leads people to be at greater risk for the development of Type I hypersensitivity.

In addition, we as physicians should all be concerned about both of these as a unit in that we have to understand that the integrity of universal precautions really depends on a number of different things. First of all, the skin really is the most important barrier to infection and anything in the gloves that impedes somehow the skin's ability to block the transit of blood-borne disease really leads to a downgrading of universal precautions, rather than maintaining them.

Third of all, products that are causing problems for the health care worker are products that are not going to be used. And in order to have good universal precautions procedures, we really do need to have products that are available, that work, but also will be used by the consumers, who are in this case the health care workers.

I realize now that I forgot to give the preamble

appropriately. My name is Jay Slater. I am at Children's National Medical Center. I am in receipt of research funds from Safeskin Corporation.

As you have heard many times, there are several different adverse reactions to latex. We are not going to talk about the erdant(?) type. The Type IV reactions actually have been described way back and the original article was from 1933 in The New England Journal of Medicine. It is an extremely common type of reaction both among health care workers and among any workers who are constantly exposed to the chemicals in these gloves. That, of course, is the reason that this is such an important concern.

Here is a picture of a patient with contact dermatitis, the cracking, irritation. It tends to be a more chronic type of reaction. In contrast, the Type I hypersensitivity reaction is an immediate reaction that can lead to a full range of reactions from mild contact urticaria to anaphylaxis.

The very first report of Type 1 reactions actually was from the 1920s in the German literature. But it wasn't until 1979 that some reports appeared in the European literature and it wasn't until the late 1980s that two

groups in North America, our group at Children's and a group in Toronto, began to report episodes that had occurred in the United States.

The FDA Drug Bulletin Report of October 1990, you heard about that this morning already in one of the other presentations and, again, the FDA Medical Alert in March 1991 were both prompted by reports of severe, life-threatening and in a couple of cases fatal reactions that have been reported to these -- to latex in devices.

Now, again, the full range of IgE mediated reactions to latex is exactly as you would predict from other types of IgE mediated reactions and that is the mildest form is contact urticaria. Systemic urticaria is a frequent consequence of latex exposure in susceptible individuals, rhino-conjunctivitis, bronchospasm and in the most extreme form, anaphylaxis.

This is a picture of a patient with urticaria on the hand, presumably contact urticaria to a glove product. The anaphylaxis is fortunately the least common of the latex-induced reactions, but it is by no means a rare occurrence. These are data from the FDA, from the four year period of October 1988 to September 1992. These are data that are entirely generated by self-reported cases. In

other words, as you are well aware, there is no regulation that requires anybody to report latex-associated anaphylaxis. These are episodes that were so severe that the practitioners that observed them felt the overwhelming urge to pick up the phone, figure out how to report this to the FDA and then go ahead and do so.

Nonetheless, you can see that during this four year period over a thousand episodes were reported and the lion's share of these were reported due to latex exam gloves, barium enema catheters and surgical gloves. A very small number here, an 11 -- I am sorry -- in the yellow bar, these a research 11 deaths that were reported during this period, all of these due to barium enema catheters.

Again, you have heard mention this morning about high risk groups. These include children with spina bifida, health care workers, rubber industry workers and there appear to be some other risk groups that are of lesser significance. Dr. Whitehouse, you asked earlier about how these data were generated. And the fact is they were generated in a number of different ways.

The best studies of spina bifida groups were actually done by the New England Myelodysplasia Association as a survey of various myelodysplasia clinics around the

country in which the surveys were backed up by skin tests or by blood testing to confirm sensitization. Those data range between 0 in one clinic and 28 percent in another clinic.

In general, most of the data that you will see will be IgE seroprevalence data; in other words, surveys of sera in which latex rasts(?) are performed. And when it has been looked at in a controlled manner, the actual clinical sensitivity is about half of the seroprevalence sensitivity.

So, in those studies in which 15 or 20 percent of people have been shown to have IgE specific to latex, somewhere between 7 to 10 percent of those patients are actually clinically sensitive. Interestingly, and very importantly, as many as 50 percent of patients who are latex allergic are also allergic to one of these and any of a number of other fruits and some vegetables as well. So, this allergy not only has implications in terms of your ability to undergo medical procedures, in terms of your ability to maintain your career as a health care provider, but also sometimes your ability to eat.

Now, the natural history of latex allergy and health care workers, I think, is a key point that we need to understand. The most frightening piece of data for me as an allergist is that as many as half of people, who end up

developing anaphylaxis go from a completely asymptomatic state to anaphylaxis on their first exposure. That means that if you take all of the people who have anaphylaxed to latex and you question them rigorously about previous episodes, half of them will blank out completely and will have no idea from any previous episode that they were allergic to latex at all.

So, as an allergist, this is the number that frightens me the most. As people concerned with contact dermatitis, this is the line that should concern you the most and that is that a substantial portion of these patients appear to go through a phase of having contact dermatitis to latex chemicals first.

We don't really know whether this reflects an actual stage at which these people are at increased risk or whether it is just the same people that tend to develop contact dermatitis as will go on to develop the Type I latex allergy. But certainly it is biologically very plausible that if you break down the skin barrier, you will be more likely to absorb the protein antigens that lead to the more severe systemic reactions.

Once you make the diagnosis of latex allergy, it is an untreatable disease. Avoidance of latex allergens is

the only method that has been shown to prevent latex-induced anaphylaxis. I am speaking to you now as somebody who spends the vast majority of my own research career trying to develop other modes of treatment. We know that premedication doesn't work. There is no way you can prevent a latex-induced reaction by premedicating somebody with antihistamines or steroids.

There is an immunotherapy protocol currently going on in Europe. It is generally considered to be a very high risk antigen to which to submit patients to allergen immunotherapy, although this is the protocol that is currently going on and we are all eagerly awaiting the results of those studies.

Epitope-based studies, DNA vaccine studies, these are underway in animals at this point and I speak to you as somebody who spends a lot of time working on these specific issues, that none of them at this point has been shown to be of any value whatever. So, when you think about modes of treatment of latex allergy, in your list of four, the first three are avoidance and the last one is a very vague other.

Again, once you make the diagnosis of this disease, as far as we can tell, it is a life-long disease. We are not aware of anybody who has spontaneously remitted

from having latex allergy. I didn't mean this to be an inflammatory talk in any way and I just want to close with the same points that I started with and that is that the reason to talk about Type I reactions in the same breath as Type II reactions are basically three.

One is there is some suggestion that they are biologically connected; in other words that one leads you to be at greater risk for the other.

The second is that both of them break down the likelihood that the skin is going to be a good barrier to the transit of blood-borne pathogens and the third is that both conditions lead to a decrease in the likelihood that health care workers are actually going to use these barriers effectively.

Therefore, I think, applying good, high, understandable and biologically sensible standards is extremely important.

Thank you.

DR. SIMMONS: Thank you.

We will go on to our next speaker. Let me apologize, too. I think at the beginning I said that we should be stopping our speakers about 2:30. I think that would be about 3:30. But, hopefully, we will be finished

much earlier than that.

Our next speaker will be Dr. Timothy Sullivan, who is a well-known allergist in the area particularly of latex, from Emory University.

DR. SULLIVAN: I am Tim Sullivan. I am a physician in the discipline of allergy and immunology and a professor of medicine at Emory University School of Medicine in Atlanta.

The rubber tree itself, have a braziliensis is tapped and the sap is processed into rubber products. And as you know very well, chemicals are added for various purposes and still take polymerization to facilitate preservation, but it is a tree sap. By weight, gloves have very small amounts of these low molecular weight but highly reactive chemicals that are of concern about context and activity. They are between 1 and 2 percent by weight protein in the finished glove, which is pretty amazing.

Between a half and 1 milligram of protein comes out for gram of glove. What is a gram of glove? It is something on the order of a three inch by three inch square. So, very substantial amounts of protein come out of the standard latex glove.

In hospitals, because people are taking gloves off

particularly, but putting them on and using them, substantial amounts of the protein antigens are found circulating in the air. How much of the low molecular weight chemicals accompany them isn't known.

By inhalation alone, much less percutaneous exposure, people working in hospitals have very substantial inhalation of proteins from the rubber to the extent that you are approaching an annual pollen exposure just by working in a hospital for a day or two.

So, if you express delayed hypersensitivity, poison ivy-like reactions to chemicals in rubber, then you get a sight of contact problem. If, instead, you express IgE antibodies, as Dr. Slater has set the stage, then these antibodies attach to tissue cells, called mass cells, that contain and release histamine and many other mediators, upon exposure to the gloves, then you get the following.

These cells rapidly release inflammatory molecules that can cause itching, swelling and inflammation of the skin and then clinical manifestations of this are itching, hives, swelling. If it hits the eyes and the nose, we have inflammation in those tissues, occupational asthma, as Dr. Slater point out, anaphylaxis.

The point that people who are exposed to natural

latex gloves, particularly in an occupational setting, may have itching and swelling on the basis of delayed hypersensitivity, on the basis of IgE antibodies, on the basis of both. And, indeed, it is this context of a person working in an occupational setting within immunologic consequences that we are talking about. That is why we are setting a broader context.

But it is the IgE sensitivity, which can kill you. It is the contact sensitivity issue that we are addressing this afternoon, but there is a much broader context and I think it is very important to deal with that.

How does one establish the diagnosis if the contact sensitivity is made with perhaps testing primarily IgE sensitivity? People who have inflamed hands when they wear natural rubber latex gloves are at risk but by no means certain to have IgE antibodies or delayed hypersensitivity.

Those who have occupational rhinitis, asthma, contact urticaria are more likely to have IgE antibodies. Again, this is far from certain.

The history of allergic reactions to other latex exposures can be helpful. Dental procedures, delivery of babies, surgical procedures and direct contact with rubber products, other than rubber gloves, can give you some clue

as to the presence of sensitivity.

For IgE antibodies, one can either take blood and look for these antibodies in the serum or alternatively we can present latex proteins into the skin, see with the naked eye within 15 minutes an inflamed allergic reaction in the skin, which clearly goes on when people work occupationally or the same antigens land in the eye and the lungs and so on.

Well, now, the question has been raised as to how many people have this sensitivity and how bad is it and it is very important to realize that the detected antibodies found in general populations have very different implications from those found in occupationally-exposed people. This was a study we did two years ago, facilitation of operating room nurses when their meeting was in Atlanta.

There were greater than some 7,000 people who attended the meeting in Atlanta and we offered information and testing for latex sensitivity. Those who had clear cut, by our estimation, allergy, had blood drawn for confirmation and otherwise weren't tested, were given information, but those who were either curious or had ambiguous histories were tested.

I had colleagues come from Milwaukee to help out

along with our fellows. This is important. We took natural rubber latex gloves, soaked them for 15 minutes, 1 gram into 10 milliliters of saline; 15 minutes later took the rubber out. I can't imagine that is too different from a sweaty hand up against the glove for a short period of time.

We had 28 people out of quite a large number we tested who had an immediately weal and flare positive skin test. Ten of them had allergic reactions to the skin test so badly, we had to give them epinephrine and I think Dr. Fink(?) and Kelly and I needed tranquilizers.

The point is that we tested with much too high a concentration of antigen. We provoked anaphylaxis in ten people out of 28 who had antibodies. But the point is a nick on your hand, washing your hands and putting on gloves is not very different from the test we performed. So, my point is pretty obvious. This is one example, that IgE antibodies in an occupationally exposed person repeatedly exposed carries with it a significant risk of anaphylaxis. Important amounts of protein are absorbed.

Now, we have roughly 3,000 personnel working at Emory University Hospital and we have screened them in part by an annual interview in which questions are asked that would raise the possibility of latex allergy. Then they

have been studied by the contact sensitivity or for IgE antibodies.

The main point here is contact urticaria, which is depicted here, of those people who reported having itching and swelling of the hands right after putting on a glove, only 20 percent had detectible IgE antibodies. As you go up here, if you had hand dermatitis and had allergic rhinitis and asthma as well, there is about an 80 percent chance that IgE would be found.

If you had contact urticaria, rhinitis, asthma, then you were 98 percent likely to have IgE antibodies. But the main point here is a lot of people with rhinitis, asthma and contact urticaria in the occupational setting do not have IgE antibodies and, in fact, many do not have -- in the case of those skin problems, do not have delayed hypersensitivity. I will get back to this issue in a minute.

So, it is common that there are quite a few things at play in here. Now, an estimate of somewhere on the order of 1 to 6 percent of the general population was offered as the possibility of what in the general population are people marching around the sensitivity to latex. We really don't have good data on the prevalence of delayed

hypersensitivity, to low molecular weight chemicals in natural rubber latex products, which are the subject this afternoon, but even among people prone to contact sensitivity, the estimates are -- they are somewhere on the order of anywhere from 2 to perhaps as many as 10 percent of people with that proclivity reacted to those molecular weight chemicals.

IgE antibodies on the other hand are found in somewhere on the order of 1 to 10 percent or so of the general population. But we don't know what that predicts in terms of disease. I make a point about occupationally-exposed nurses, if 10 percent of them had IgE antibodies, then their risk would be really quite remarkable. But in the general population, we don't know.

We just finished a study at Emory where we tested 500 people with allergic rhinitis and asthma, but no occupational exposure and 2 percent had IgE antibodies as assessed by skin testing, but only had nearly died of latex anaphylaxis.

I might comment that she had been told by her physicians that the two episodes of anaphylaxis she had on two occasions, while she delivered two different babies, were attributable to on the one case antibiotic, another to

an opiate. It turns out that wasn't quite right.

Among people with allergic rhinitis and asthma, various studies have estimated that 2 to 6 percent are carrying IgE antibodies to latex. What that translates to in disease isn't know. Two surveys of dental personnel, one came up with an estimate of 6 percent, had clinical latex allergy. Another survey had 8 percent.

The various studies that have looked at prevalence of skin test reactions, immediate skin reactions, the hospital personnel put the estimates, as you heard, from 5 1/2 percent to over 17 percent. Some studies, asthma because of latex proteins is estimated to be about 2 percent, one study 6 percent and so on.

In spina bifida patients, you have heard that some of these data pertain to the presence of IgE. Other data pertain to clinical disease, but these children, these people have very high level of both antibodies and disease.

Now, why dwell upon IgE again? Well, the point is this is the context on which you are trying to make decisions about what to put on a box that says "hypoallergenic" and while one antigen causes contact sensitivity and another kills you with anaphylaxis, I can tell you already there is a tremendous amount of confusion

among patients and even medical personnel about a box that says "hypoallergenic" and they put the gloves on and don't do so well.

Let's do some numbers here. From Jonah's book, which estimates the work force and other resource, 1992 data presented a year ago, depends on how you define health care worker, but it is on 11 million people. It is estimated 10 percent of the American work force of health care workers. Frequent glove use is estimated to occur in at least six million people, in hospitals, nearly five million physician and dental offices, another two million people with frequent rubber glove use during the day. This is a very substantial number of people, of course.

Now, if we just pick a number, say, 1 percent of people in the general population have IgE antibodies, we are talking about 2 1/2 million people. Among those people who use those frequently in an occupational setting, everywhere from police officers to firemen, ambulance drivers, all the way up to surgeons, then that is over 500,000 people.

The number for people working in hospitals is 8 percent. That is nearly 400,000 people, occupational asthma occurring in nearly a hundred thousand people. So, we have got lots of people at risk already from IgE antibodies and

some of those folks also have great hypersensitivity as well.

Among the health care workers, what are we up against? If a doctor, a nurse, a dentist, a dental technician or others with occupational exposure to natural rubber latex then becomes a patient, which is inevitable, they have the risks of contact sensitivity from tape to anaphylaxis when they try to deliver their babies or have surgery or have dental procedures.

In addition, Dr. Slater made the point it is not so great to have hand dermatitis. You have a poor barrier function, which means you are more likely to have bacterial infections, which means you are more likely to transmit them to your patients, but also any patient material that gets onto your hands is much more likely to penetrate, in any case not so good.

In addition to that, IgE antibodies can mediate occupational asthma, rhinitis, conjunctivitis. Do you really want your neurosurgeon sneezing? And then there unquestionably are systemic allergic reactions primarily mediated by IgE antibodies by current lights. So, this is a serious business.

Career-ending sensitivity, you have heard one

example attributed to contact sensitivity and IgE sensitivity can do the same thing in some people under current conditions. Well, it is perfectly obvious from an allergy point of view just -- and your grandmother, too, would say, look, we have a problem here. Let's do something about it and primary prevention deals with preventing the generation of either contact sensitivity or IgE antibodies and this is what your guidelines are set up to deal with, but I think by narrowing the focus down strictly to delayed hypersensitivity will need some thought.

In any case, evidence that you don't -- sensitization is what you are seeking and I think that is very desirable. Once people are sensitized, though, you don't want people having reactions, whether they are lymphocyte mediated in the skin or IgE mediated all over the body. These people are common -- and by anybody's estimate, anywhere from 5 1/2 more likely to 10 percent of the people working in hospitals, doctors' offices, dental offices are sensitized and many of them are having disease when they go to work. We have to figure out how to stop that.

The status quo can't continue. And then you have to find people who are actively sick because of their latex sensitivity, deal with their hands, deal with the rest of

their bodies. And you notice we are really not doing that. That is not the task of this committee, but on the other hand, it is the context in which you are trying to make decisions about, among other things, what kind of a label to put on boxes as "hypoallergenic."

If you look at physicians, there are over 600,000. Each year we turn out another 15,000 medical students. Estimates from Canada say that when they enter the medical students aren't allergic to latex. When they graduate, 8 percent have IgE antibodies to latex. A similar study in Germany said that when the dental students graduate, 13 percent have IgE to latex and their medical students in the same center, 14 percent.

We are constantly putting people into an environment, which is continuing to sensitize and elicit disease. Nurses are much more numerous. We are turning out some 82,000 nurses each year. I didn't put in the dental personnel, but the point is every year we are sending new people into the same setting.

Occupational asthma related to latex has come of age and in the recent review of occupational asthma, latex was among the more common causes of occupational asthma. The criteria are the presence of antibodies, in this case,

airway reactivity and changes in airway function when exposed.

Many will go on to have impairment or disability. Look at this. If somebody has asthma related to allergy to latex, this is the standard of care. Either you change their work environment or they must stop working in that work environment. That is the standard of care. This is serious business if you happen to be marching around IgE antibodies to latex and you have an asthma because of it.

How often does this occur? Well, here is one study published two years ago. Somehow they persuaded 94 percent of the personnel working in this hospital to be tested. Five percent had IgE antibodies to latex. Of the 13, they persuaded 12 to undergo testing and 12 of 12 had abnormal reactivity to histamine consistent with asthma.

Seven of the 12 when they inhaled dust from gloves had 20 percent fall in the ability to move air in the first second or greater, indicating that they certainly did have asthma related to these particles.

Overall, then, the estimate was 2.4 percent of the people working in that hospital had occupational asthma because of latex. There are a couple of other studies. One study put the estimate at 6 percent. The main point is this

is a very large number of people under current working conditions.

Now, to Joan McColby's(?) data in 1987, which she collected in roughly 1985, she looked at 512 employees in her medical center on people who used gloves frequently. She found 2.8 percent had positive skin tests, indicating IgE antibodies were present. They had disease when they wore gloves. She noted, of course, that she could predict who these people were because they had had hand dermatitis before or they tended to have allergic rhinitis or asthma in the past, also frequent glove use.

Just a non-selected occupationally-exposed group, .8 percent had positive tests for IgE antibodies. In the operating rooms, more people had antibodies than those outside the OR, but the point was she detected antibodies, but the only disease that she noted in these patients were skin problems. They didn't seem to have been having other reactions to latex.

Now, this is a bit ephemeral, but the notion is if you say that in 1985, when that study was done, you would estimate that some 2 percent of the work force had IgE antibodies, as assessed by tests we continue to use. There were roughly 1 billion gloves used in the United States that

year and the -- arbitrarily, we have assigned a unit of 1 to the severity, indicating that this was -- as best it was understood at that time among occupationally-exposed people, a skin problem and more of a curiosity than anything else.

Ten years later, then roughly 10 percent of the work force had detectible IgE antibodies, five times as many. We now, as Dr. Slater pointed out, have people having anaphylaxis under various latex exposure conditions and 1995, something on the order of eight billion gloves were used.

I understand that last year it was somewhere on the order of ten billion, but I am sure representatives can tell us, but there has been a massive increase in use. The number of people using them have increased. The number of gloves used per person have increased and at the same time, increasingly severe allergic disease has been detected, attributable to these antigens and quite a sizeable number of the work force has these antibodies.

DR. SIMMONS: Dr. Sullivan, could we have a summary, please?

DR. SULLIVAN: Yes, we are getting right there.

This is as good a place to summarize it. In 1995, the College of Allergy put out a position statement

summarizing the published data. That was two years ago and there is just tons more since. They pointed out this is obviously a major problem. The word "epidemic" is appropriate. Certainly, the frequency among health care workers is greatly increased compared to other people.

The severity is intense, sometimes fatal. So, it is important. There are ways of dealing with this that could avoid the cost of disability and risks and so on. The status quo won't get it. NIOSH has just put out what is called a latex allergy alert in which they summarized the published data, included these data as well as the last two years and came to the conclusion that powdered latex gloves really should no longer be used.

Addressing the IgE issue, at least that improves air quality, but my point really is that the context in which you are trying to make a decision is one in which there is an epidemic among health care workers. There is an endemic among other people. This is very important and what kind of immune response is only something of a detail.

So, I would just argue that while much is going to change the gloves that are being used, for example, they may not use the powdered gloves much longer. These are reasons why. This is the context that I think I would urge you to

be very careful about what words you put on packages, which might lead or mislead people in terms of safety.

DR. SIMMONS: Dr. Sullivan, before you leave, I am not sure that we got a statement from you at the beginning of your discussion about your financial interests.

DR. SULLIVAN: I have done no research sponsored by glove companies, have no financial interest in any manufacturer of any device known to man.

DR. SIMMONS: Thank you. Thank you for your discussion.

We will go on now to our next speaker and I want to make sure I am saying this right. Dr. Wava Truscott. And Dr. Truscott is the vice president of scientific affairs of Safeskin Corporation. She has a Ph.D. in pathology. We have already read her conflict statement of interest, financial statement.

DR. TRUSCOTT: Thank you very much for all the speakers. It has been a great opportunity to listen to all the different views, especially in the Type I, a very, very serious type of allergic reaction.

As we meet today, we are talking about the Type IV reaction, which is extremely important to the panel, I know, as we discuss what type of labeling is required, what type

of testing is required in order to verify that a glove, which contains chemicals will not cause allergic dermatitis or for those people who are already allergic, will not cause them to elicit a reaction. Those are the two things that we are going to be looking at right now as I go into my talk.

Also, as we go on, I would like to explain, too, that latex has been a phenomenal advantage, a phenomenal boom to medical devices in general, as far as an excellent barrier and I don't believe that we should throw away the baby with the bath water until we truly understand what we are doing.

There have been a lot of studies of people going over to vinyl, for instance, and there have been a lot of barrier problem issues. This is very near and dear to my heart, as my brother is going to have to undergo his second liver transplant due to hepatitis from the health care setting. So, it is very important that we keep everything in our thought processes as we go on and keep levels of chemicals and levels of proteins and levels of any type of contaminant low on this medical device we call a medical glove, so that we don't sensitize the population so that barrier then becomes a very important issue.

As we go into discussion, notice I did discuss a

little -- to say a little bit about synthetic gloves. Gloves whether they are synthetic or they are latex contain chemicals. To make a latex glove, for instance, takes about three days if you don't put accelerators in it and it is the accelerators themselves that can cause allergic reactions. So, there is a lot of manufacturing then. A manufacturer must slow the line down, must construct the formulation so it has lower amounts of these accelerators, choose the ones that would be the least possible causing of an allergic condition and also would undergo special processing afterwards, such as washing with special neutralizing systems afterwards to get rid of the chemicals in order to earn the right to bear a low chemical type of claim.

That document was presented by Dr. Tomazic this morning.

So, as we discuss this, I would recommend that in the document itself it does state latex gloves, natural over latex chemicals. This really should be a document that is expanded to all gloves, all covering of the hands because the chemicals in nitrile(?), for instance, are exactly the same chemicals in a rubber glove, except you switch the natural product of polycysisoprene(?) units from the tree. This stage, you use a nice elastic polymer or I should say

chemical called acrilanitril(?) butydyane(?). Otherwise, all the other 50 or so chemicals are the same that you would have in a latex glove.

Vinyl has different things, such as thialates(?) that can cause issues. In fact, it is about 50 percent of thialate as a plasticizer. As we go on then, I would like to recommend, number one, that the document be included -- we include the discussion of synthetics, as well as just latex.

I am afraid I am in black and white. So, it is not quite as exciting here.

For instance, in Japan, where 50 percent of the gloves used by house care workers are vinyl. The other 50 percent is latex. If you go to a dermatologist or there are a couple of publications from Japan -- and this has been in use for many years -- that 50 percent of those problems with gloves that -- allergic contact dermatitis caused by the chemicals are caused by vinyl and 50 percent by latex, another issue that we must include both synthetic and latex.

The 1994 FDA contact sensitivity task force, Dr. Bob Rietschel at the time explained that he had had not that high percentage, but he had had also allergic contact dermatitis caused by synthetic gloves.

Just examples of the types of chemicals we are talking about. We want to prevent conditions, such as presented by Dr. Shapiro this morning. Anyone who would like copies of any of these overheads, more than welcome to.

Now as we go on, I would like to talk about the patches themselves. As specified in the document that the patches have been one by one and, indeed, they have been a combination of one inch squared, but also a two centimeter squared, the problem being that the special -- and Dr. Maibach will address this much better than I, but the type of patch test that is used is actually the Webril -- is it Webril is how it is pronounced, Dr. Maibach?

DR. MAIBACH: Perfect.

DR. TRUSCOTT: All right.

The patch uses a two by two, where it will not be able to occlude and seal in a one by one. There have been many studies written that actually determine that, yes, there is a 40 percent reduction in the dose delivered, but in this type of a study, a patch test study, it is the concentration rather than that surface dose that is going to make a difference.

I have copies of those but since Dr. Maibach has done some of that research, I am sure he will present it

much more in the more reviewed literature.

Much more important than that is the number of exposures. And I appreciate, coming from -- as a manufacturer and paying the cost of this study, which will increase from about $40,000 if you do both of them, will be well in excess of approximately 160, 180,000 dollars, that the reduction to nine is going to be a big help, but, indeed, it is more important to the number of times repeated exposure rather than the surface area covered if the concentration is the same.

So, if it were to be changed so it had to be even more sensitive, I would recommend more exposures, if necessary, although nine is plenty as far as convenience and expense of the study.

The switch from 200 person to 300 percent, historically this has not shown a huge difference in the number of reactions that have been viewed. It has shown -- let's see, I think -- Frank, help me out -- Dr. Jordan studied how many individuals? You are going to make me look it up --

PARTICIPANT: [Comment off microphone.]

DR. TRUSCOTT: All right. There were only two positives out of thousands and thousands of individuals. I

think you are right, 2,400 individuals -- 2,411, thank you.

However because of the increase in the statistical relevance, I know that our company would certainly support that. After all, this is the cream of the crop, the better glove. So, I believe, although we haven't seen it different historically, it will increase the statistical significance. So, we will certainly abide by it.

Once past the threshold level, the contact may be of less significance. That is when we are talking about the one inch -- two centimeters square.

Also, in the 25 sensitized individuals, at first this seemed like a tremendous number for me and I was just shocked. I didn't think that we could possibly find that number of people for number one. Number two, I wasn't certain it was necessary once a person was sensitized to really have 25 people to be tested.

So, I asked the statistician because I am ashamed to say I am not a statistician and they explained to me the difference in the upper and lower limits. If everyone had to be negative, which they do in this particular already sensitized individual test, the 25 people recommended, that if you only used 12, which is the number I was looking at, you may have out in the general population 22.1 percent of

those individuals could show a positive. And it would still have fit in the test. It would not have been a false test.

If you go to 25 individuals and all of them turn out negative, then you can have the assurance that there would probably only be 11.3 percent that might still be positive in that specialized sensitized population. So, it probably is worth it for, again, for this cream of the crop to reach that degree of sensitivity.

However, I have a question on that. What happens when you do not add the research mecaptobenzothiazole(?) or the thiazoles to your product. Do you then need to test on individuals who have mecaptobenzothiazole? I would say "no" because as far as I know there are no breakdown products or issues. It is in your 510(k) that you do not use it; thus, you cannot use it or you are in breach of 510(k). So, I would recommend that if you are not going to put it in there, that the manufacturer then would so state in his 510(k).

The only question would be in the instances where you do not add thiuram, but there is a breakdown in your carbamate, which could potentially occur in some circumstances, which it has to be assessed by either chemical analysis or -- and I would prefer not -- testing on

25 individuals.

As I have talked to some dermatologists, although it is possible to have the two groups, the thiurams and the carbamates, it may be very difficult to have the panel on the mecaptobenzothiazoles, at least in some locations. And along those lines also -- oh, I would request that if we are to increase to 300 individuals from the 200, that that should probably also be considered for cosmetics and every other type of test that uses the Draize Study that is under the auspices of the FDA, rather than exclusively to gloves.

Also, geography, it is now required that we take our test and split it, 150 people in one locale and 150 in another. I realize that that does increase the diversity of your test population. I know that there have been some studies that I have read, where switching, as Dr. Maibach has, switching from a caucasian group to a more diverse population has not shown any difference in the predictive capability of the test.

However, logically, I have to admit since guinea pigs do show a difference between species, that you certainly could have -- or strains rather, you could have a possible difference. Does that mean then that the other hundred that we would have to do for those people who have

already done 200 on their Draize Study would have to split that test into two locations? And is there evidence that states that we really do need to have two different ones?

On the interpretation of sensitivity scoring, it says that out of those 300 people, not one individual can have a score of plus one or greater. I really do disagree with that. It is too easy, if you are wearing a patch for 72 hours occluded and you have taken a shower and you have done this and you have done that and your kids hit you in the arm and this has happened and that has happened and it is occluded, to have an irritation caused not by the glove but just by circumstances. You don't wear a glove for 72 hours. It is not true to life.

In this study, remember, we have already done the animal testing to show that we are not going to cause irritation. This test is supposed to look for sensitivity and in my feeling then, irritation should not be counted and plus one can show an irritation.

Also, it is required that -- and I wasn't quite sure of this, but it is required that if you do find a presensitized individual in your first -- in your induction phase, that must be reported in the 510(k). I understand that for gathering information. I would just request that

it not be used -- held against us as far as the product itself, since these people are already sensitized and the test is for people who are not sensitized.

Now, on the labeling, I am going to suggest something that might be just a little bit different. There are three types of chemicals, as we already discussed; the mecaptobenzothiazoles or the thiazoles, the thiurams and the carbamates. Those three accelerators are the biggest problems. I would request that those individuals who -- companies who choose not to take the cream of the crop, not to go the extra mile and develop gloves that have the low chemical, so specify which chemical they have in their glove. It would be something like specify the presence of any of the following chemicals, thiurams, thiazoles or carbamates, so that as an individual does have a problem, they will know where to go.

Now, remember, since this 300 people is going to be looking for many things, it won't be just the Type IV -- I mean, the three accelerators. It will be looking for other catastrophic or changing chemicals that might have occurred. So, that is going to be more of a benefit than just these three. But, at least all gloves then you would have a safer feeling of knowing which chemicals are or are

not a problem.

For those who go the next step and do the testing on 300 individuals, I would suggest that they still have the chemicals from the specific list because there are going to be sensitized individuals that are grabbing a box of gloves, but they also go ahead and do the modified Draize, two to three hundred people, depending upon which is determined, and that they can go ahead and have their label.

I don't have the cautionary statement that has not been tested on sensitized individuals only because I neglected to type it on there. It should be on there.

Then, of course, for the last group, since they have been tested on sensitized individuals, the labels would not -- you would not have a chemical ingredient list required. You would have the 200 or 300 person Draize label claim. However, you would not have the warning statement, has not been tested on sensitized individuals, because it has. And you would follow with the label that it has been tested on sensitized individuals.

Notice, I have both of them. It wasn't really clear in the document whether you could have both. I believe it is important because a person needs to have some sort of a realization that they are not going to be

sensitized as well as people who are already sensitized that they can wear this glove. Just for user friendliness, I would like to have a two or three word introduction to the sentence, something like reduced sensitization potential and reduced reaction potential.

Significance -- this last overhead -- I know I am on time here or getting over time here -- for the significance level of chemical residuals, we discussed in 1994, that the ideal is a chemical test. We can only test people or test animals so long. We were trying to go away from that. We need to find a threshold on the thiurams -- or I am sorry -- mecaptobenzothiazoles, a .01 percent was determined to be a safe level. We need to determine that also on the carbamates and on the thiurams so that we can move away from human and animal testing, except for catastrophic chemicals, there will probably still be some sort of a Draize test.

Depending on the chemical residual for claims at that point, you would be able to move away from the 25 individuals, after you determine which threshold they are reacting at and build a database, of course.

That is basically what I wanted to hit -- oh, I know, there was one other thing. When we talk about gloves

now, more and more gloves are built with lubricants or site specificness, such as a coding, so that when we do the Draize test, we really do need to specify which side of the glove we are testing on, so that we are testing what the wearer would actually have, unless, as a medical device, we are also considering that that wearer will also be a patient one day, but that is a little different consideration and will probably take a different type of meeting.

But it needs to be site specific when it is on contact with the dermis, epidermis.

Did I hit it all? User friendly -- oh, and the other thing was a phone number. That was another thing CAT(?) covered in the 1994 meeting, which I believe is very important, that all of us manufacturers should have a phone number so that if someone -- say they are allergic to paraphentyldiamine(?), which is in the glove, which doesn't cause it as much as the other three, but they may not know that and they may not understand it. Perhaps that phone number would make a difference to help them walk through identification and diagnosis.

Thank you very much. I appreciate your time.

DR. SIMMONS: Thank you.

We have our next speaker, Dr. Frank Perrella. Dr.

Perrella is speaking for the American Society of Testing Materials. Could you please give us your name, your affiliation and any financial interest you may have, any new medical device.

DR. PERRELLA: My name is Frank Perrella and I am representing the technical committees that aim to alert the contact dermatitis and counsel sensitization. My financial interest is I work for a medical glove company, Tillotson(?) Health Care.

I would like to also talk about allergic contact dermatitis and chemical sensitization and some of the things that have been done with ASTM, the American Society for Testing and Materials.

First, I would like to just give you a brief background of what ASTM is. It was established in 1898. The American Society of Testing and Materials is one of the world's largest voluntary standards development organizations. ASTM provides a forum to develop national consensus standards.

The ASTM technical committees are open to the public, government and industry. An ASTM standard is a document that is developed with the consensus principles of the Society and meets the approval requirements of the ASTM

procedures.

Although these standards are voluntary, they are used by government agencies to specify their requirements. The ASTM committee responsible for rubber is D11, which was originally formed out of the need to develop product tests and specifications.

There are two specific ASTM committees that were formed that are related to these particular issues. One is the D11.40 Chemical Sensitization and the other is the Human RIPT Patch Test Working Group, which were both formed at the request of FDA and industry.

The process by which standards are developed within ASTM are there are people that have certain expertise that get involved and volunteer their time. I volunteer my time as chairman of these two committees.

First, there needs to be a request for a new standard, such as in this case, a request from the FDA and from HIMA to form a chemical sensitization task group to develop an analytical test method that could be used for labeling claims of being below a certain threshold of chemical residuals for thiurams, thiazoles, carbamates.

The other was a request for a Repeat Insult Patch Test for human clinical studies, so it could be standardized

for gloves so that all manufacturers would conduct the test in the same manner and that the agency would be able to review the study that is done in a uniformed standardized way.

So, a task group was established. We then determine what is known. ASTM usually doesn't discover anything new. We take what is out in the world, what manufacturers and other scientists and clinicians have been using, what works for them and then we apply it to see whether we can actually write a standard and validate it within ASTM so that we have something that across the board for a particular product one would conduct according to a certain protocol.

So, a draft is then proposed. A standard is proposed. It is written up based on what is known. If it is an analytical test, round robin testing is done through many iterations of trying to validate that proposed standard or draft. The data is reviewed. It is revised and at some point down the road, it is then submitted to the subcommittee of ASTM, which is a broader subcommittee of many products and it needs to meet the approval, needs to be voted on and needs to meet the approval of that subcommittee.

If, in fact, it is approved through that subcommittee, it can then go on to the main Society ballot, which is extremely broad within ASTM. That is beyond the realm of even medical devices. So, there is quite a process to approve a standard. It goes through many iterations.

Next, I would like to mention that there is a public law. With the passage of the Technology Transfer Improvements Act of 1995, the Food and Drug Administration requires all medical gloves to conform to specific ASTM standards. In general, other than certain exceptions, all federal agencies and departments shall use technical standards that are developed or adopted by voluntary consensus standard bodies, using such technical standards as a means to carry out policy objectives or activities determined by the agencies and departments.

This is similar to some of the standards, for example, the Repeat Insult Patch Test that is developed. This is from the National Technology Transfer and Advancement Act of 1995, Public Law No. 104 to 113.

Some of the standards that exist for medical gloves, the base general standards that give the specifications for a medical glove, are for exam gloves, ASTM D3578, for surgical gloves, D 3577. You also need to

know that these are not -- these are like living documents. They get revised. They are revised every few years and could be up for revision at almost any point. And they are always going through iterations of improvement.

There is also a separate standard for vinyl examination gloves, ASTM D 5250. There is currently a draft in its final form of the nitrile examination glove that could be approved in the near future.

So, chemical sensitization or what was known in the past as hypoallergenic claims, some of us have used the term at least within our group as reduced chemical sensitization for seeking a shorter group of words that not -- might be specific for chemicals, as opposed to reduced sensitization potential, which could be sensitizing from anything.

So, we use the word "chemical." Another thought on this was some were in favor of just using the ASTM standard and saying simply, rather than to get confused with jargon, allergy sensitization, elicitation, to just say it passes the ASTM standard for the Draize period. Or if we had additional ASTM tests, we could say it passes the test and that would be labeled on the package.

It certainly would be easier in 12 languages than

a statement of 30 words. So, the claim implies that the glove will result in fewer allergic reactions, the Type IV allergic contact dermatitis, than gloves that do not merit the hypoallergenic label.

It does not mean no allergic reactions. The test does not assess Type I protein allergic reactions, as you have heard previously.

What I would like to do is just step you through what does a glove have to go through now, what is usually submitted to the FDA and what you need to know. There are some tests that are done prior to human clinical studies. These are the primary skin irritation tests. It is a test that is designed to determine the dermal irritation potential of gloves to intact and abraded skin of the rabbit. That is ASTM F 719.

Another ASTM standard that is used prior to submitting for human clinical studies is a dermal sensitization test. The test is designed to determine Type IV immunological response potential of gloves to the skin of guinea pigs. It is ASTM F 720. These are existing standards that are in use; also, is used as a patch test called a Buehler Method in Archives of Dermatology.

In addition, the International Standard

Organization, ISO, has a document, a standard document called Biological Evaluation of Medical Devices, Part 10, that describes both irritation and sensitization in animals. These are done for medical gloves.

Now, taking that, what have we done to this point? At the request of both FDA and industry, a group was formed within ASTM to look at chemical sensitization or at least an analytical test on the one hand to measure residuals and on the other hand, to try to standardize the clinical method for patch testing above and beyond rabbit skin irritation, guinea pig sensitization, then human Draize.

We have now today an approved ASTM method as of June 1997 for a human repeat insult patch test, ASTM PS 77-97. The test method is to determine reduced chemical sensitization potential. ASTM Human Repeat Insult Patch Test Working Group, the working group was established again at the request of FDA and industry in 1996.

Within about six months time, we wrote and approved this test method in a very short period of time. ASTM PS 77, the modified Draize repeat insult patch test is designed to determine the potential of a glove to elicit Type IV immunological responses in at least 200 subjects. The active participants in this working group were Drs.

William Jordan, Howard Maibach, Robert Reardon and myself participated in writing and reviewing the standard that is currently approved.

Let me go through some of what we have done, taking into consideration what the FDA had outlined in a template prior to that. We went from -- for gloves, instead of -- I shouldn't say traditional -- gloves were done by both 24 and 48 hour patches. They weren't done any one way. So, taking this as one base way it used to be done, 24 hour patches, one day of rest for the skin, another 24 hour patch for nine or ten inductions was about a 12 day non-cumulative patch. There is one day of rest in between and a 24 hour challenge. The ASTM method went to the more stringent 48 hour induction, nine inductions, which is equivalent to a 21 day cumulative patch test.

It is only removed for scoring and then placed back on again. There are no skin recovery periods fundamentally. It is a 48 hour challenge as opposed to a 24 hour challenge and read 48, 96 hours after application. The experts in dermatology, Drs. Jordan and Maibach, supported this approach. We set up our own scoring system that was similar to what has been used and the FDA has accepted that scoring system.

Let me talk just a little bit about the scoring system because it is part of this discussion of what is a pass or fail. Allergic contact dermatitis reactions are associated with more pronounced erythema and edema, typically, than irritant contact dermatitis and have a greater tendency to form small vesicles or blisters.

Allergic contact dermatitis has a tendency to spread beyond the areas of primary contact. This erythema reaction without any significant edema by some, according to their submissions, have been submitted as question marks, plus signs or some with erythema and edema have been submitted as a numerical score plus a plus sign after it.

These are used by some in different ways for different interpretations because of -- at least in the glove submissions -- a lack of standardization of the protocol. So, we tried to standardize it. But one plus reaction present at the initial 48 hour reading but which has faded to a questionable response or has disappeared at the delayed reading of 72 to 96 hours can sometimes be a false positive reaction and must be interpreted cautiously, according to the Manual of Allergy and Immunology, which you can't see there.

Patch test reactions with intensities of 2 plus or

3 plus are almost always truly actions. It didn't say 1 plus.

So, just briefly, to look at some of the things that have been out in the field for submissions for gloves, some have been a question mark for doubtful or minimal response, a plus, plus-plus, plus-plus-plus for erythema and separate scoring for edema for irritation. Others have been a plus, plus a numerical score, 1, 2, 3, 4 and then a separate scoring for edema. Others have been a 1 plus, which is erythema and edema all in one score, 2 plus or 3 plus.

What we adopted was a numerical score so that submissions would have one numerical value of a level of what would be a criteria of a pass or fail. In addition, we included edema, papules, vesicles and so on and gave them an additional .5 score, so that a 1 reaction with an edema, an erythema with an edema, would be not a 1 plus but a 1.5. So, essentially, similar to our scoring within the ASTM PS 77, a 1.5 erythema and edema is very similar to a 1 plus in the scoring system of combined erythema and edema.

Also, this is -- the references on the bottom, there is a reference here from irritant contact dermatitis, a Howard Maibach edited book. We have come to understand

that water alone can provoke an inflammatory reaction. Irritation can occur from sweating underneath occlusive surfaces of gloves. A study was done by TKL Research. They took 27 subjects, human subjects, applied patches that were wetted only with water. And out of the 27 subjects, 6 out of the 27 had scores of 1, 22 percent of them.

A second independent study was done on the human clinical. Just water in the watch, an occlusive patch, and 8 out of 29 scores gave a 1 score, 27 percent. Occluded water or sweat can elicit a skin reaction response of 1 in a human patch test.

So, ASTM PS 77, which is an approved standard, a voluntary consensus standard, recommends a sample size of 200 subjects and not a sample size of 300. As stated in ASTM PS 77, if the sample size is increased from 200, which is what was done in the past, what is done by cosmetic industry and is more traditional, the 300 subjects, and there were no responders in the test panel, then the maximum permissible reactions to the population would change only from 1.5 percent to 1 percent.

What that means is there is a difference of only a half a percent. The repeat insult patch test is not sensitive enough, in our opinion, to pick up a change of a

half a percent in the population. That is would justify going from two to three hundred in this somewhat subjective and semi-quantitative test.

Changing the panel size from two to three hundred subjects does not nothing to significantly improve our yield but will certainly increase the cost to the manufacturer, a quote from Dr. Robert Rietschel of the Department of Dermatology at Ochsner Clinic in New Orleans.

So, further, ASTM PS 77 recommends a more typical Webril patch of two by two centimeters, which is available commercially. There isn't a one by one centimeter patch available, to my knowledge. It applies adequate pressure to a thin film and since it should be equivalent a response to a one by one inch patch, we recommend the traditional two by two centimeter Webril patch.

In addition, the FDA 1996 Glove Guidance Workshop booklet recommends a two by two centimeter patch. ASTM PS 77 recommends a minimal skin reaction sensitization score of 1.5. I might add that dermatologists, at least the feedback I got, they wanted a higher score on this to be a positive reaction for sensitization. So, 1.5 was the minimal that we thought and not a lesser score of 1 because occlusive water patches can produce a score of 1.

ASTM PS 77 recommends a sample size of 200 subjects, since increasing the sample size by 50 percent does not enhance the sensitivity of the test. We also recommend the selection of subjects between the ages of 18 and older with no age exclusion above 65. Typically, these clinical sites or locations that do this test have people that are retired. It is not unusual for retired people to go in for patch testing. In fact, the original draft of the ASTM PS 77 had 18 to 75, I think, and Dr. Maibach recommended that it was removed because it was biased to age. We so did. We removed it at the request of Dr. Maibach.

ASTM PS 77 recommends a minimum of 100 subjects per clinical location. It is not unusual to do lots of a hundred subjects at a time, to have 200 subjects at one clinical site and one or the other or vice-versa.

Next, I would like to inform you that there is a Chemical Sensitivity Task Group that was put together at the request of both FDA and industry to develop an analytical test that determined the residual chemicals of thiazoles, thiurams and carbamates in medical gloves that could be used to identify a sub-threshold level that could be used for labeling things in place of clinical studies on sensitized

individuals.

So, the objective is to develop this analytical test of residual extractable accelerators for this claim of reduced chemical sensitization or whatever it becomes in the future when that is decided on.

The test method is designed to look at aqueous extractable accelerators in rubber products and right now we have draft methods under development and we have meetings periodically, including we have a meeting this Thursday in Philadelphia at ASTM headquarters. We have drafts for reverse phase, high performance liquid chromatography and a colorimetric assay for dialkyldithiocarbamates.

A detection limit of this is about 10 parts per million. Our objective was to keep it down that low because it looked like the literature was saying .01 percent below which you start removing reaction. So, we took a hundred parts per million and said our analytical test should be sensitive below a hundred parts per million.

This method -- this task group has been in existence since 1994.

I have a couple of overheads and if I can just bring this up and show you. This is just -- this is from the last FDA workshop and Dr. Robert Rietschel was the

moderator at that meeting. He also wrote two letters to me, one about a year ago, as an ASTM chairperson of the Chemical Sensitivity Task Group, and asked me to submit it to the FDA, which I did, and just recently has written me another letter in response to the FDA's hypoallergenic and labeling.

I thought this was appropriate because he was the previous moderator of this working -- the last workshop and it is to myself, chairman of the ASTM Task Group on Chemical Sensitivity in the Draize Repeat Insult Patch Test.

"Thank you for sending me the latest information on the FDA's plan to what has previously been called hypoallergenic gloves. I am very concerned about the wording that has been proposed by the FDA. I do not believe that a lay person will understand the labeling. Back in 1994, when I chaired the workshop on this problem, I had proposed that the labeling be very specific. I had suggested that the label read 'safe for those sensitive to mecaptobenzothiazole, mecaptomixthuiram(?) carbanates.'

" I pointed out that only individuals who will specifically benefit from these formerly hypoallergenic gloves are those sensitive to rubber accelerators named on the label. The only way people can determine that this is their problem is to have been referred to a dermatologist or

allergist for patch testing, which would routinely be capable of identifying these materials as allergens.

"These are patients who are a target audience for this type of glove. We had suggested that chemical analysis of the glove material, which a working group was formed at ASTM, showing that gloves are free of these agents should have sufficed and suggested that a negative PAP's(?) test in individuals shown to be positive for these materials would be a simple way to confirm the safety issue.

"I still stand by these previous suggestions. The lay public does not understand the induction of sensitivity -- this is in regard to the label of maybe 30 some odd words. Induction of sensitivity and the elicitation of sensitivity in trying -- that is label 1 versus label 2 -- in trying to develop wording that deals with this technical issue is in my mind misdirected.

"Those individuals who actually have a sensitivity are the ones that need help in finding a way around this problem. The labeling I propose eliminates the word "allergy," "hypoallergenic," "induction," "elicitation" and does not even mention latex. The wording I propose is specific and can assist people that have documented allergy of this type.

"The FDA's emphasis on proving the Draize test is in my mind misplaced. There is not a sufficient body of evidence that the proposed changes will actually increase the sensitivity of the Draize test to the point that it will improve public safety. Dr. Robert Rietschel, Chairman of the Department of Dermatology, Ochsner Clinic."

DR. SIMMONS: Dr. Perrella, may we have a summary, please?

DR. PERRELLA: Yes, I will. I might add that Ann Baldwin of HIMA has given me half of her time.

This is another letter that Dr. Bill Jordan --

DR. SIMMONS: Could you just -- one second, please.

How much more time do you think you are going to have? And is Ms. Baldwin here?

DR. PERRELLA: No more than ten minutes.

DR. BALDWIN: I am going to need about maybe five, six minutes at the most.

DR. SIMMONS: Okay.

DR. PERRELLA: Dr. Bill Jordan was an active participant in writing PS 77-97, the ASTM Repeat Insult Patch Test. When I was looking for expert dermatologists, I went to someone at the Cleveland Clinic and they told me to

go to two dermatologists and only two in this country. One was Howard Maibach and one was Bill Jordan. And they were the two dermatologists that I went to.

Bill spent hours and hours and so did Howard on the phone with me. Bill Jordan couldn't be here. He is involved with important clinical, but he wrote this and asked me if I would submit this. He was part of this ASTM working group. So, I think it is certainly pertinent for this group.

I would like to address the proposed panel site of 300 subjects, the size of the patch and the lumping of the irritation scores. He goes on to say that the quote of Henderson and Riley, which has to do with the statistics of the 95 percent confidence limit, this assumes more than we actually know about gloves used in panelists. I will share my latex testing experience since 1988 to the present.

To find one sensitization to latex gloves has produced over five to seven years, it would take nearly a thousand volunteers. My laboratory has conducted 14 different human repeat insult patch tests for five major domestic suppliers of latex gloves since 1988.

Two thousand four hundred and eleven volunteers were used to test 24 different latex samples. A half a

million dollars was spent to discover two subjects out of 2,400 tested for allergic contact dermatitis. Four subjects from a volunteer population were found to have preexisting ACD. Two subjects had contact urticaria. The testing protocol in these human repeat insult patch tests used the more rigorous double 48 hour challenge phase and sample sizes of two by two or one inch patches.

Dr. Jordan goes on to say the reason increasing the panel size is not immunologically valid for this test is that the test rises and falls to the occasion, based on concentrations present. The test is about inducing allergy dependent on concentration. The finished product may be a fair representation of some of its ingredients but totally lacking in validity for some of its other ingredients.

All published studies for validating the usefulness of the repeat insult patch test has stressed the role of examining a range of concentrations of a single half centimeter and its relationship with its vehicle. Finished product testing is not totally useless, but it can rarely disclose the sensitization potential consistently with a mild to moderate sensitizer when test concentrations of that ingredient are less than .5 percent.

The test can discover gross errors in formulation

of newly-generated allergen not intentionally added. Ranking low order allergenic finished formulations as even less allergenic, hypoallergenic, based on current induction and elicitation methods cannot be accomplished by another half centimeter impact size or another hundred people.

I point out that we uncovered twice as many rubber glove delayed allergies in the open population than we created. The appendix 1 of the FDA's proposed draft he discusses, the only published studies on that matter agree that size is of no importance unless the area is very small. Concentration for unit area determines sensitization rates. This was first proposed by Snitzer(?) in 1942. Magnuson(?) confirmed the findings in Klugman's 1966 classical paper on the factors of influencing induction and elicitation, allergic contact dermatitis presumably addresses these issues.

The only time size may be important is if the area is very small, such as a quarter of a square inch. There is commercially available patches based on two by two Webril. They are not available for a one inch patch. He addresses the scoring system, one plus irritation of scores observed during any phase of this test for allergic reaction have no meaning, other than a notation by the observer.

One plus is the mildest observable erythema and useless it is put in context with a control or as part of an individual collective repetition. A 1 plus on a 48 hour occluded test doesn't say anything about a product's potential to irritate in a real setting.

Finally, Dr. Jordan says allergy tests are one thing. Irrigation comparison tests are another. It is possible to do both in the same test but you need to allocate a separate slot. Scattered 1 plus reactions are so common under conditions of the test, they can only be taken seriously under very defined circumstances.

If you patch test nothing but the test device, that is, without the glove specimen or, as I have shown with water in it only, you should still be confronted with 1's, plus 1's and even plus 2's on occasion. The FDA's approach is that this would be a failure for the glove if you had a 1 plus. That is why we think it should be graded the score.

The modified Draize is a very valuable test, but it is all too frequently forced in predictive situations that make those who have written about it and refined it shudder. Moderate and highly sensitizing compounds are likely to be found in finished products, substantially near zero defects would call for draconian alterations in the

test.

So, basically, this really supports that I in looking to the experts have not found, other than a biostatistician looking at statistics, which in my mind is different than real life empirical data over the years gathered, have not been able to gather information to justify an increase from 200 subjects to 300, that this would provide any greater safety to the user.

I have not found any evidence in trying to look that a glove should fail on a score of a 1. At a minimum, it should be a 1.5 and to some people's feeling, it should perhaps be higher if, in fact, we are talking about sensitization. I don't think we should discriminate against age in this clinical study for clinical sites and locations and I think at this point, diversity of the population by having two clinical locations, basically, you get diversity just by default, by the people that walk in the door.

It is a combination of men and women, Hispanic and aside from the black population being excluded by the dermatologists because of a harder to read, the skin reaction.

Thank you very much.

DR. SIMMONS: Thank you, Mr. Perrella.

I think right now I am going to ask Dr. Maibach if he would like to do his presentation now. I think you have a plane to catch.

DR. MAIBACH: Actually, the HIMA, if it is only five minutes, I am in great shape.

DR. SIMMONS: Is that okay? You are going to give us five minutes? Okay. We will go on.

And we have a schedule change. Ms. Ann Baldwin.

MS. BALDWIN: Yes. I am Ann Baldwin, director for technology and regulatory affairs at the Health Industry Manufacturer's Association. And other than the salary that I draw from HIMA, I have no other financial interest to report to you.

I just have a very brief statement that I will read into the record.

The Health Industry Manufacturer's Association is a Washington, D.C.-based trade association and the largest medical technology association in the word. HIMA represents more than 800 manufacturers of medical devices, diagnostic products and medical information systems and within our membership are manufacturers of medical devices containing natural rubber latex.

HIMA has been active with the FDA and the

scientific and clinical community for many years to try to determine the best way to communicate to customers the appropriate selection and use of natural rubber latex medical products with respect to their levels of relevant manufacturing chemicals. HIMA is concerned that the labeling language that is proposed in the draft guidance is confusing and unworkable.

The statements appear contradictory. They are too long and unwieldy, particularly for multilingual package labeling and they are potentially confusing to users of the products. HIMA, therefore, makes the following recommendations: One, FDA should adopt without revision the recently released ASTM standard for the modified Draize test, PS 77-97.

Two, FDA should ask and work with ASTM to develop and establish a method for patch testing with glove pieces those individuals who have Type IV hypersensitivity.

Three, with ASTM standards in place for both the modified Draize and the patch test, manufacturers should then be permitted in lieu of the proposed wording in the guidance to state on their labeling that the product meets ASTM PS 77-97 and/or the applicable ASTM numerical designation for the patch test.

Four, manufacturers would then take responsibility for training the user community about the use and correct interpretation of the relevant ASTM test methods. These recommendations have the following advantages. The references to the ASTM test methods are concise and clearly identified to package the product attributes. There would be no confusion as to which test criteria the product meets.

The approach is consistent with FDA's current labeling requirements for labeling of protein levels using the ASTM modified Lowry(?) test method and finally the approach is in keeping with the intent of Public Law 104-113, the Technology Transfer Improvements Act of 1995.

And with that, I will close my remarks.

DR. SIMMONS: Thank you.

I am going to ask you to please give a copy of your statement to the transcriptionist.

Oh, yes. Now we will go on to Dr. Howard Maibach. I hope I am pronouncing that right.

DR. MAIBACH: Any way you would like.

DR. SIMMONS: He is professor and chair in the Department of Dermatology in the University of California.

Please state your name, your affiliation and your financial interest.

DR. MAIBACH: Madame Chairman -- an interesting paradox --

DR. SIMMONS: Yes, it is.

DR. MAIBACH: -- panel members and I assume, at least the United States world of interest in these ten billion gloves, condoms, balloons and everything else made out of latex.

I have been given an assignment and I will do it. First, you must know my name because it wasn't clear. Howard Maibach. I am a dermatologist at the University of California and I assure you that the ASTM nor the Tillotson Corporation offered me nor did I accept an honorarium for the use of my name in those slides.

Second, nor do I have any other financial interest that I am aware of.

I was given an assignment to cover a few of the facts as we understand them and I will take the liberty, as have the other speakers, to make a few fortuitous comments that are not factually based that might help the consumer in the end.

The first question that is brought up is where did the late Dr. John Draize, one of the most prestigious and accomplished government scientists that any government has

ever known, where did Dr. Draize get the number of subjects. Where did he get the size of the patch and what do we know about it?

Well, you must understand that everybody in this room doesn't know what to do. That is clear, if you have heard any of the presenters. We have learned something but most of what we know has been learned subsequently to when the non-ASTM Draize test was written. Now, we have reviewed with a lovely medical student, who is now a resident, Monica Upadye(?) -- the reference is in your handout -- the total world experience as to how you would choose the size of the patch. For those of you who want to go through every detail of it, it is in the reference. I will only give you the highlight.

This is the data in which a group of animals were -- no, I am sorry -- group of human beings were exposed to dynitrofluorobenzene(?) and they were then challenged at various doses per unit area. You don't need to go through the details. You don't need a first rate statistician to see that those standard errors do not show a difference.

This is now the same information expressed in which you are looking at different sizes that the same mass was exposed to. Again, if you look here, although it looks

like there are slight differences, the key point is it is the mass per unit area and it is not the size of the patch.

Now, what you need to know is in the debate about whether it should be 2.54 centimeters by 2.54 centimeters or one inch by one inch or two centimeters by two centimeters, whatever you want to ask, the answer is we at the moment don't have an experimental basis to answer it. What I showed you was data and what the whole Upadye paper about is data with very powerful allergens in very special experimental circumstances. We don't know it for the chemicals in rubber gloves.

So, you may choose to debate many, many ways of making the decision, but it is certainly not going to be based on science because we haven't generated the experiment. Could we generate the experiment? The answer is "yes." We could have done it at a far more cost efficient manner than all of these meetings. So, that takes care of the issue, the size of the patch.

Now, the second issue that has been brought up that I have been asked to comment on is does the universe of dermatologic allergists or dermato-toxicologists have any data that would help the rubber industry and the agency who are just helping the rubber industry in this event decide

how you do this 25 percent test to find the non-eliciting dose, the dose that will not produce clinical disease in homo sapiens exposed to rubber gloves.

Well, we don't have an enormous experience. I mean, I can't give you 5,000 chemicals that we have done it for, but I can't give you 5,000 chemicals that I think are allergens. But we have the model worked out. It is a cost effective model and this is the type of data that you get.

To make this a little more interesting for those of you who were here at the last meeting, I chose to take some new data for formaldehyde worked out by Torqlamenty(?) and his colleagues in Copenhagen. They looked at something that we had looked at before and they found that if you take a look at patients, which are the ones that we would identify as being allergic to a thiuram, if you take a look at those patients, we screened them with a single application with a very distinct patch at 10,000 parts per million.

The threshold depends upon the degree of reactivity; namely, those people that are supersensitive will clearly have a different threshold than those that are less sensitive. But if you take a group of subjects commensurate with what is being recommended here on

statistical and practical grounds, the threshold for the panel that was studied here was 250 parts per million.

So, obviously, there is a very big difference between the dose that you use to identify the allergen in a test patient that you think maybe sensitive and that necessary to elicit it if you want to do dose response curves.

But for the rubber glove consumer, there is another fact that we clearly understand and which is driven clearly in the data with formaldehyde. If you take this particular panel and you actually use the formaldehyde-containing foundation mass or anything that you want to preserve with formaldehyde, you get a very different story because there is a very simple test that we have used for decades now, but is now being validated and standard, known in the United States by me as the provocative use test, but since the best validation data comes from Finland, the name that I put on this slide is the repeat open application test.

No matter what you want to call it, the test is the same. You take people who are putatively sensitized on a single patch test and then you have them use the product in miniature. To decrease the risk to de minimis, you

miniaturize the test. You don't put this cosmetic used here over the whole body. You choose a site. The most sensitive site happens to be the upper back, but the cubital fastra(?) is more convenient into the laboratory and the volunteer.

If you do a repeat open application test with an actual product containing formalin, the threshold at 300 parts per million, nobody reacts. Now, since there are one or two people in this room, including one of the panel, who we are trying to get to use the word that we are dermato-biologists, this was done on the forearm.

If you took the same amount of formalin and put it in your excilla(?), the threshold, which we have worked out and Bill Jordan has worked out, is 30 parts per million. So, what I am really sort of trying to suggest is that, yes, working with panels of sensitized subjects has enormous power compared to the Draize repeat insult patch test.

So, using these assays is going to forward the cause, decrease the cost for the industry and increase the result of confidence and credibility for the consumer. We know how to do it. I know a number of people who have responded to some of the agency's documents, have called and said, Howard, there aren't 25 people in the whole world who are allergic to these things.

Well, clearly, that is nonsense. Joe Fowler will get you 25 tomorrow and I am being lazier than he is. It might take me three days. If these things were so rare, we wouldn't be here today discussing Type IV sensitivity.

Now, before I go into the next area, the ASTM document is better than the other guidelines that existed before, not necessarily through my input, but I would like to sort of -- because I have got you in my hands, you are my captive, let you understand that any proforma document of this is just a bare summary. It is not a substitute for a laboratory director, who knows the principles to figure out what is going on.

When you patch test, you are, in fact, studying the ability of an immunologic system to work but you are also studying the ability of skin to demonstrate the immunologic fact. That is known as the elicitation phenomena. Just, Joe, to make this interesting for you, this is from one of my young colleagues in the current issue of the Korean Journal of Dermatology. I hope all of you read it regularly. I know I do because, in fact, the figures are always in English, which makes it easy.

This is the data now, taking various amounts of mass and changing the size of the chamber. Without going

into the details, you can see the data varies all over the place. So, in fact, you really do have to standardize all of this in a very specific type of occlusive system.

Now, I am going to leave the slides and now I am going to go to a few of the other things that I was asked to comment on, plus my one or two fortuitous statements and you can withhold my honorarium for having made them. I cannot emphasize enough -- I don't know what I can do, other than do cartwheels, to tell you that the practicing physicians of America, our entire health care system is ten years behind you people in this audience.

They don't know the difference between Type I. They don't know what Type IV is about, including many of my dermatologic colleagues. They are not taught that. They certainly don't know the role of irritant dermatitis in gloves. So, whatever we do, if any of us are going to be part of the solution rather than the problem, we have some big time educational efforts.

For those of you who are interested in education, maybe this is a conflict of interest. I might get a tenth of a penny per book. Some of you may know that there is a standard textbook. It is used widely, especially in Japan and Europe, much less so, unfortunately, in the United

States, on the science of protective gloves, the safety and efficacy. It is called Protective Gloves. It is from our laboratory and it is in your handout. But I think tomorrow afternoon the same publisher, again, from our laboratory, is releasing a book on the contact urticaria syndrome and there is an enormous amount about latex, the most up-to-date papers on the latex human situation for Type I. But no matter how many books you may write, it is your job to somehow let the public and the medical public know about it.

Next, I cannot emphasize that the -- we have left out a very important factor. Frank hinted at it, but he backed off. I guess his boss wanted to be sure we didn't make it anymore complicated.

The Draize test can be made far more powerful by going back to senior high school or freshman year of high school chemistry; namely, you can extract the allergens and in some of the Draize repeat insult patch testing, it is extracting the allergens that allows you to make the identification that you want.

All of you who work in biocompatibility are fully conversant with extractions. There are some special problems when you deal with materials like gloves, but many of these have been worked out. I will be happy to give you

the references, but don't forget that if we are now looking at sensitized subjects, we are looking at thresholds in sensitized subjects, extraction offers a very powerful tool.

Everybody has mentioned the role of damaged skin, but two things have been left out. Please remember that one out of every twenty people in this room, not biologically, but statistically, because we have the numbers, have hand eczema. Most of that hand eczema is probably endogenous. It is from within side of you. But also, they buy gloves and use them. So, that has to be factored in to how powerful we make our labeling and our assays.

Please also remember that it has been dodged around like people playing dodge ball, but in reality many brands of rubber gloves are irritating and, hopefully, the next generation development will be gloves that are truly hypoirritating for those consumers who can't use the regular ones and who are not allergic and don't have Type IV sensitivity. But the irritation certainly compounds the clinical problem and, therefore, we need to make our safety levels even higher and more careful.

Now, when you get to the Draize test, you heard in Bill Jordan's letter, you heard Frank say that mass per unit area is critical; namely, if you wanted to look at those

slides that I showed you, the few experiments that we have suggest that I could take everyone of you and put you into the bath tub in this Holiday Inn with poison ivy, poison oak and poison sumac and I could be a god. I could determine which of you get poison ivy and which ones don't.

It is simply a matter not of the amount that you put in the tub. It is the amount that gets in each area. If I lower the dose, none of you will have a problem. If I put a lot of the poison ivy in an area of 1 centimeter, you are going to get or most of you are going to get poison ivy, poison oak or poison sumac.

We understand that. Draize didn't know it, but intuitively he was correct. So, in fact, the Draize repeat insult patch test and all of my colleagues in the Skin Division at the agency know about it, gives you false negatives ad libitum and we will get false negatives here unless we do a great deal of thinking. And Bill Jordan said he has tested 2,000 people. He got two positives. That just shows you how weak the assay is.

So, let's not give up on it. Let's make it stronger. One way to make it stronger is to try to maximize the amount per unit area. The agency is thinking that this is a matter of size. It may be a matter of extraction. It

may be a matter of having two layers thick, but I don't think we have even tried to solve the problem.

Of the last several products approved by very clever colleagues in the skin group, topical group of the agency, two of the materials have essentially withered in the market because they were such powerful allergens. The reason that we wouldn't know this is it was run at too low a concentration.

So, you really have to do a little bit of thinking of how you design the test. The anatomic site is not a matter of flattery or what part of the body do you want to show to the laboratory. We know the most sensitive site is the upper back. So, clearly when these tests are done, we have to get some way of translating to the laboratories that are doing it that we know the correct anatomic site.

The scoring has been totally confused today. If there is anybody in this room, it is certainly not me, who knows the magic number, please identify yourself because you are much smarter than I am. Please, the numbers are just for discussion. The numbers are communication.

I don't speak Hungarian. I had lunch today with my lovely Hungarian daughter here at the hotel and we decided that we needed a common language. She speaks

English. So, we spoke English, not Hungarian.

The scores, you have to know the biological event they are describing. If you are talking about the weight gain of a rat in a rodent study, everybody will agree it is milligrams, grams, helograms, micrograms or picograms. The scores that I heard bantered around today mean nothing. You must simply say that we want to use numbers, but this is what the numbers mean.

Please, when the meeting is over, go to my colleague, Dr. Fowler. He will explain to you that for decades we have known that an allergic reaction in its full form will have erythema or redness and edema. So, no matter how the final regulations are written, we have to get that idea across.

Now, the fact that you see erythema and edema alone is not sufficient. It is required but not sufficient because there are many things that will occasionally produce erythema and edema; namely, a strong irritant in this test will produce erythema and edema and you will call it an allergen.

So, the enlightened dermato-allergist today, whether he is in Louisville, Kentucky or whether they are in Japan or in Europe, none of them that I know about, who call

themselves dermato-allergists and who do experiments to try to validate the clinical meaning, none of them call that allergy anymore. What they do is they say this is erythema and edema. They give it a code so we can do our statistics and counting, but then they have a very simple algorithm to determine is that erythema and edema due to the vapors? We call that a rogue reaction. You know, we don't know how else to explain it. Or is it due to allergy?

There really is a nidus of individuals available in Asia, in Europe and in the United States that will help you take what John Draize had to do arbitrarily and convert it into medical science because today we really have done the correlation studies to know when erythema and edema means allergy and when it doesn't mean allergy.

Madame Chairman, I hope I have stayed within my time. Whether you choose to penalize for my fortuitous comments about education, please do so because you are the chairperson.

And then lastly, we don't know it all, but we really do know a great deal and we would be very happy, my colleagues in dermatology and allergy and immunology, to try to help in any way we can, the consumer and the -- the ultimate consumer deserves the best break we can give them.

Thank you.

DR. SIMMONS: Thank you. Before you leave, you referred to a document, a handout. I don't think the panel members received that.

DR. MAIBACH: Well, I received a copy of the current ASTM document, which I thought the rest of you had received and I think if you spoke to Frank, he would be happy to provide massive quantities.

DR. SIMMONS: Okay. We do have it. Thank you.

Now, I think we have finished this part of the presentation and we have about 20 minutes that we want to know leave for the panel to discuss, ask questions of the speakers.

If we still have some speakers, you may want to identify yourselves to let us know you are still in the room and we are going to open it up for about 20 minutes to ask you questions and then we are going to take a break, about a five minute break, and then we are going to come back and go through the discussion phase of this meeting.

Yes.

DR. PERRELLA: Is it possible to make a comment now? I just wanted for the record to mention -- for the record, this Frank Perrella. Neither Dr. Rietschel or Dr.

Bill Jordan or Dr. Howard Maibach have participated in any testing for Tillotson Health Care or have they received -- they have not received any financial support for any of the participation. They have done it in the spirit of ASTM and volunteered their time.

DR. SIMMONS: Okay. Thank you.

We now will open up this meeting for the next 15 to 20 minutes for questions that the panel have of the speakers.

Panel members. Yes, Dr. Edmiston.

DR. EDMISTON: Dr. Maibach, I have a question.

With the Draize test, if one increases the sensitivity, the predicted sensitivity, looking at an index and if we choose 1 plus or 2 plus as an index, and we also increase the size of the patch to the current available patch size, can we see a greater increase in sensitivity by using that approach?

DR. MAIBACH: As in my brief comments, I will give you the science and then I will give you an opinion. The opinion is clearly fortuitous.

We published with Frank Marzuli(?) at the FDA, 20 years ago, and it is in the ASTM handout, that if one likes to beat down straw men, you can beat down the Draize test

with great ease. Many authors have done it. It is silly. Draize didn't know the role of concentration.

Today, I can take any new dermatologic drug and I can give you a false negative, unless it is a very powerful allergen, by running it at use concentration. If I want to get a real insight into what Draize was talking about, a warning sign to do a risk assessment on, then I have to go up in the concentration.

So, let me give you an example. Neomycin is now available over the counter. In order to sell it, it is usually sold at under 1 percent concentration in most countries. In order to identify that it is a moderately potent allergen, which it is, about one out of every hundred consumers who use it gets dermatitis. And this is field epidemiologic studies.

I have to run it at 5 percent. That is the problem. So, it is concentration dependent. Now, where we get in the awkward and embarrassing stage for rubber gloves is while we have been talking about this for years, neither myself -- and I hope myself just as responsible as anybody else -- nor anyone at the agency nor industry, which I had hoped by now would be motivated to do the question, to answer this, have found a way to increase the concentration

of these additives.

Now, I am guessing that it is doable. Therefore, if you admit that this is such a weak test, which it is, using the final product, that is where the second stage of the agency's recommendations will be so helpful because, in fact, the second stage is like that provocative use test that I was mentioning, the repeat open application test. That will allow you to do what is in parlance today in general toxicology and dermato-toxicology, that is what is known as the risk assessment.

DR. EDMISTON: Can I turn this around and ask my colleague a question, Dr. Fowler?

DR. SIMMONS: Yes.

DR. EDMISTON: Dr. Fowler, if you look at 200 or 300 individuals who are having the Draize test, and they were using a 1 plus threshold, how many of those would be reactive?

DR. FOWLER: I think that all depends on what is being tested. I am not sure I understand your question.

DR. EDMISTON: Well, going back and looking at the handout here, I saw that on page 8, it says skin reactions in individuals who are already allergic to one or more of the following classes of chemicals, thiazoles, thiurams and

carbamates. And then the next paragraph under test subjects --

DR. SIMMONS: Excuse me. Are you referring to the guidance document?

DR. EDMISTON: Yes.

-- positive diagnosed to be allergic to each of the above classes of chemical sensitizers in natural rubber. If an individual is just sensitive to one of these and you applied this test, as opposed to someone who is sensitive to these and you applied the test, in your experience, what would be the result?

DR. FOWLER: I have to see if I am following your question. And by the way, I think, as Dr. Maibach said, these numbers are not hard science, like weights and measures. These are bioassays that are looked at by the human eye. So, the importance is the definition of what a positive test really is and whether we call that a 1 plus or what have you, but we must know what that positive test really is.

I suppose that you are probably asking if one subject is allergic to only one of these chemicals and a second subject is allergic to all three and if all three are present in that glove piece, then is it more likely to get a

stronger reaction in that individual who is allergic to all three than in the one who is allergic only to the one? You know, intuitively, you might think possibly so, but, I mean, again, that depends probably on the levels of each of these chemicals in that glove sample or presence at all. As was mentioned before, one of these allergens may not be used at all in some gloves.

I will expand on that a little further in that most individuals that we see for testing are allergic to both carbamate and thiuram in the -- the same individual is very commonly allergic to both so that the actual use situation would be likely to find that a high percentage of these 25 subjects would be allergic to both thiuram and carbamate. If they are allergic to either one, they are usually allergic to both. I won't say usually, but often.

So, I can't really answer. I mean, after having said all that, I am not sure I can really answer your question as to what would be expected, but I think the result of a positive or otherwise -- you know, the relevant result we are trying to look for, a true allergic response, would still occur at the levels great enough to cause it to occur.

DR. EDMISTON: The data that was presented by

Perrella -- did I pronounce your name correctly -- showing that just water, water that is almost encapsulated, will cause a positive response.

DR. FOWLER: Now, there, you are looking, though, at more of the Draize methodology, rather than these people who are already sensitized. You know, those are kind of apples and oranges a little bit.

DR. EDMISTON: People who are already sensitized, who if they were -- just received the patch, would they have any response at all if they just received the patch plus the water and no chemicals? In other words, are they --

DR. FOWLER: In other words, would you do a negative control, is that what you are saying, if there was something without the piece of glove, but just a negative control?

DR. EDMISTON: Yes.

DR. FOWLER: Sure, that is usually done in most of these studies. And would they react again? A small percentage may react with some perceptible reaction, but that is where we differentiate. Whether we call it a 1 plus or a 2 plus or whatever, you know, it is important to differentiate the morphology of that non-specific reaction, which, in fact, is usually very weak and, you know, this is

a bioassay. There is not a perfect scientific difference between the two.

DR. EDMISTON: [Comment off microphone.]

DR. FOWLER: Sure. We have never done it. And, unfortunately, some dermatologists would also read a 1 plus different than another. But in general, there is fairly good understanding and uniformity of what constitutes a true allergic, important allergic reaction.

Again, whether we call it a 1 plus, 1 1/2, whatever.

DR. SIMMONS: Any other questions for our speakers from the panel?

DR. WHITEHOUSE: Madame Chairman, could I ask Dr. Sullivan, I think -- is he still here? -- about your view on the use of hypoallergenic or reduced chemically sensitive -- reduced chemical sensitization? Should those terms be abandoned, not used at all?

DR. SULLIVAN: I think it is a worthy goal to try to lower the amount of chemicals being delivered to people already sensitive so that they have less difficulty at work. I mean, the objectives here are very good. Also, of course, if the sensitization occurs in the work place, well, then to minimize that. There has clearly been a lot of confusion,

though, among people who have a more common illness, which is this IgE antibody mediated problem, using gloves that are labeled hypoallergenic, just simply not having enough knowledge to understand what that really implied.

So, I could only see more of the same, if the same terminology is used. There are a lot of ways of dealing with this, though, but then it makes the information very hard for the average person to interpret, but I do see problems if we use a global term to describe a narrow part of the overall allergic problems that might be associated with gloves.

DR. WHITEHOUSE: Let me ask you another question. Is it possible -- do you favor the use of testing individual allergens, chemical allergens, rather than like the thiuram -- sorry, this is out of my -- thiurams, thiazoles or carbamates and putting that on the label? I think it was Dr. Perrella, who suggested the idea that it was -- or somebody in one of the letters. It was hard for people to interpret. The lay public will not interpret things correctly. Does that make any sense just to test for thiurams or thiazoles or carbamates directly?

DR. SULLIVAN: Well, I think -- I mean, you are a very knowledgeable person and, yet, there are still

questions in your mind and you have heard some of the world's experts discuss it. This is not simple. And, furthermore, it is easy to get confused about whether they are asking if a chemical can actually sensitize a person and be a cause of contact dermatitis, which is the purpose of injecting the concentration of the neomycin as a candidate, as an antigen, versus is this person who looks like it does have sensitivity to certain chemicals going to receive enough of the chemical with this exposure to get sick?

I mean, that is really one of the objectives here. One is to prevent it from occurring. The other is to avoid disease in people already sensitized. So, in that sense, you sort of bioassay a group of people who happen to have these chemical sensitivities exposed to this glove that has a certain amount of the chemical. But the question is is it at a threshold -- is the test adequate to say what would happen over three months?

I mean, these are important questions, but as I see it, because of the complexity, it doesn't lend itself to a three word explanation on the box.

DR. WHITEHOUSE: I wonder if I could ask Dr. Maibach a question about could you sensitize the Draize test to the point where it is false positive and get some false

positives?

DR. MAIBACH: In one word, yes. But I don't think that that is our problem here. It is the other way around. It is the false negatives. But may I make, Madame Chairman, another fortuitous comment that I wasn't asked to respond to?

DR. SIMMONS: You may.

DR. MAIBACH: Okay.

Dr. Whitehouse, you are -- I understand the thrust of your question and you are in a room here with a number of people who have been living with this problem, especially the industry people, who are obviously tired of it. It is training them of their energies. But in a way we really know that the studies that have been done in the very last few years, with the Type I hypersensitivity, the contact urticaria syndrome, they are paying off. They are preventing new people, not in the United States yet necessarily, but it is certainly convincing that in Finland, which picked up this football first and ran for the touchdown and the crown of some type, as they have lowered the amount of the various proteins that they are interested in measuring the way they measure it -- and those are special technical issues -- the number of new cases seems to

be dropping.

So, clearly, the effort of the agency here to lower these levels, whether it be protein or a specific protein and whether it be what is being called here chemicals, mainly the mecaptobenzothiazoles and the thiurams surely will do the same here. But really it is at two levels; namely, the small percentage of the population that see a dermatologist. They really are the outrageously unhappy ones because very few people in a lifetime will see a dermatologist.

That is the secondary prevention that this 25 person panel will help you with. The Draize test will help you identify outrageously, egregiously compounded gloves for primary prevention. Now, as the industry becomes -- pays the same amount of attention to Type IV, allergic contact dermatitis, that they are now paying to Type I, Type IV will start to improve. We will have less and less of it. Poor Joe and I will have to go to the race track or something. We will have no work to do.

DR. WHITEHOUSE: Is it a viable idea, Dr. Maibach, to eliminate the use of latex gloves and go to some other kind of glove?

DR. MAIBACH: That is an economic matter. There

are non-latex -- there are other elastomers that are commercially available and are being used today, but I haven't heard anybody in the industry, even the few people that make them, say that that is really viable. What seems to be viable for the Type I is to lower the amount of the offending Type I allergens and it seems to have -- you know, just in a few short years, with the power of one woman in one country and a few first rate immunochemists, it is happening right now.

DR. SIMMONS: Are there any other questions?

DR. HYLEK: I actually had a question for Dr. Sullivan. I was wondering if you could comment on the immunologic response in individuals over 65? As I understand it, the immunologic response actually decreases at the extremes of age. Just to shed some knowledge for us on Dr. Perrella's statement about testing individuals over the age of 65, which would not be generalizable to the population that really uses the gloves.

DR. SULLIVAN: You ask a very important question, but I don't think a precise answer can be given. For example, over half the deaths from asthma each year in this country and also in Australia occur in people over the age of 60. So, age-corrected rate, asthma is a deadly disease

of the older person, which was kind of unexpected because it was expected it should get less severe and so on.

Certain kinds of immunologic responses in older people certainly are impaired but when it pertains to specific questions with specific antigens and either delayed hypersensitivity or the expression of IgE antibodies, I don't know the answer to that. The guess would be that they might be a little bit less susceptible, but I would have said the same about asthma.

DR. HYLEK: One other somewhat related question on the pathophysiology underlying immunologic mechanism. I am trying to understand how someone with a Type IV delayed hypersensitivity can be placed at greater risk for the Type I and if, although there has been some suggestion that that clearly occurs, whether it is because the breaks in the skin then allow exposure to these natural latex proteins. Is there really any data? Is there anything that shows that individuals with the Type IV clearly are at higher risk because I would want to be cautious about testing already sensitized individuals with these substances, if there would be any liability issues of a truly anaphylactic response, i.e., bronchospasm or hypotension and shock.

I would think it is exceedingly rare, but I am

curious if you have any numbers or percentages?

DR. SULLIVAN: Well, the data are very sparse. There have individuals described, who are called to medical attention because of cutaneous problems, who are shown to have lymphocyte mediated immunity, at least by reasonable standards and no IgE antibodies, who with continued use of natural rubber latex gloves progressed to then express IgE antibodies. But a rate, an accurate rate, has not been established and I don't think it is real reliable to say how frequently does that progression take place because you are right. There are different antigens, different kinds of immune responses and it could turn out quite variably.

As far as the anaphylaxis is concerned, I did some self-flagellation here showing you that I can cause anaphylaxis with testing, but that has caused a revolution in testing, not only in my own state, but also across the country and we start -- we can do these bioassay skin tests the same as we do with venoms to insects. We don't test with full strength venoms either anymore, for the same reason.

So, you can safely test these people as far as IgE is concerned. I don't think that is an issue.

I did want to just offer the notion that a little

over two years ago, Emory University Hospital took a hybrid approach to this problem because we had documented over 10 percent of our personnel with one kind or another of glove-related problem. Some of them have been subsequently characterized immunologically but the main point is that we made a decision to stop using natural rubber latex exam gloves. All the non-sterile gloves in the hospital are one kind of synthetic glove or another. In the operating room, about 15 percent of the glove use is synthetic. The rest is natural rubber latex because of surgeon's preference for the custom feel.

But if you do the calculations, you will find that even in teaching hospitals, greater than 95 percent of the actual glove use is non-sterile. So that we actually essentially eliminated natural rubber latex gloves outside the OR, which has had a major impact upon hand dermatitis and occupational asthma and rhinitis. In laboratories, you can't use the same kind of gloves. I am sure that a dentist wouldn't likely be able to use the same kind of polymer, but the point is that for nearly three years, Emory University Hospital has operated without natural rubber latex gloves, aside from the sterile gloves, you know, meeting standards for safety and so on.

So, that is one alternative. We are just publishing an economic analysis and it depends a little bit on what kind of a hospital you have, what your state's rate for worker's compensation is for total disability. We can make projections about costs, but elastic vinyl gloves for ward use cost less than natural rubber latex gloves. The sterile gloves are very different in their costs. So, it is an option.

DR. SIMMONS: Thank you. I think I will let Dr. Fowler have the last comment and question, unless there is any other --

DR. FOWLER: This is Dr. Fowler. I have an answer for Dr. Hylek.

In my experience, strictly anecdotal, I would suggest that on the order of half of the individuals I see who are Type I allergic to latex protein, also are allergic to these chemicals we are dealing with today, but that there is a much lower percentage that goes the other way, that those that are allergic to the chemical additives are not nearly as often going to be allergic to the Type I, the latex protein.

My question is actually an extension of yours. Probably if anybody here can answer the question about age

and skin reactivity, it is Dr. Maibach. So, I would like to have his comment on that.

DR. MAIBACH: In the handout, which, hopefully, you really will get, the ASTM, there is a reference, Pitille(?) and Maibach. I don't remember what journal, about two or three years ago. We fine combed the literature and I will give you a brief summary, but I recommend if you really need to know, you read it all.

As you get older, most young people assume -- I mean, anybody in this room under 40, I am going to call a child -- most young people -- that is you, Joe -- most young people assume that as you get older, you fall apart. We certainly all know of some pretty senile professors that we have had. So, you assume the skin falls apart, too.

Well, in fact, the skin for certain classes of chemicals, as you get older, has an increased barrier to penetration of certain chemicals. They happen to be lipophilics(?).

Secondly, that the skin of older people is clearly less reactive to irritants, but that now is using the 19th Century dermatologic viewpoint, you know, using the eye and the finger. Useful, but limited value; namely, you see less redness and less swelling. When we have studied people from

80 to 90, we have compared them from 20 to 30, there is less reactivity.

But that doesn't really answer your question, which is an experimental question. If I took a brand new allergen in 200 20 year olds and 200 80 year olds, what would happen? That experiment hasn't been done yet. But you see the difference between the two?

But the agency for other and reasons that I consider cogent reasons in the last number of years has taken two very difficult generic stances and I am not going to defend all of the thousands of scientists in the agency and at the NIH, who are as equally involved. One is that we have to get pregnant -- we need to know more about pregnant women and now infants, as you know, from Bill Clinton, and we need to know more about age.

So, it is for that reason that I sort of think it is almost outlandish today with all of the strong NIH policy recommendations to refute that in something of this -- a testing of this limited nature.

DR. SIMMONS: I will have to let that be the last word.

We are going to take about seven minutes now for a break and we will return about 4 o'clock for the discussion

portion of this meeting.

[Brief recess.]

DR. SIMMONS: We are going to spend the next 25 to 30 minutes, if needed, to discuss -- this is the panel members discussion -- the guidance document and, hopefully, we can come up with some recommendations.

Each of the panel members have been -- we have been given some discussion points. They are not questions. We are not going to go through them as questions, but they are just points to kind of help us lead our discussion, so that we can come up with some ideas or recommendations to leave with the FDA.

I have asked Dr. Fowler to kind of lead us off on this discussion and before we all leave, I will give you a chance, an opportunity, all the members, to say -- to have time to make a statement or make a recommendation.

Dr. Fowler.

DR. FOWLER: Thank you, Madame Chairperson.

I was asked also by several of the FDA members to clarify a comment earlier one of our speakers made about performing some of these tests and excluding blacks. I think that was not at all meant to be any sort of biased comment, but simply I believe the speaker meant darkly

pigmented individuals of whatever race because that is -- it is difficult technically to do a reading. I am sure that that was not directed toward African Americans or any race individually for any reason.

Let me go ahead then as you requested and go to some of these discussion topics that we have thought about. If any of the other panel members would like to make any comments, it is in the binder listed as page 1, which actually is in about the middle of the binder there, if you have it.

DR. SIMMONS: We have slides, too.

DR. FOWLER: Is somebody operating those? There you go.

The slides may not necessarily have to keep up this. Some of these there may be no comments on at all. The first several thoughts had to do with numbers of test subjects, which, obviously, several of our speakers have addressed, whether it be in the modified Draize testing or in testing of individuals already known to be allergic to some of these chemicals.

Are there questions or comments from the panel?

DR. SIMMONS: Are we talking about changing the number from 300 to 200?

DR. FOWLER: Any consensus for any modification in those numbers?

DR. EDMISTON: I think the 95 percent confidence interval is a well-established interval in medical research and I feel it is appropriate.

DR. FOWLER: Going on with test subjects and methodology, you can skip a couple of slides there. There was a question about whether in the testing, individuals with active or with other forms of contact dermatitis, other than rubber allergies, should be excluded from the testing. And the answer to that is probably if there is active dermatitis at the time that the test would be performed, those persons probably should be excluded because they are more likely to react nonspecifically.

So, large areas of active dermatitis on the test subject probably would not be a good idea.

Any other comments regarding that?

DR. WHITEHOUSE: Would that be at the site of the test, Dr. Fowler, or that would be just anywhere?

DR. FOWLER: It would definitely be at the site of the test, but even wide areas of dermatitis and other locations can sometimes cause a generalized hypersensitivity.

DR. SIMMONS: I think that their question that they need to clarify is if it is known -- if you have a known history of contact dermatitis, should they be excluded, not just for the general population, not if they have an active case at the moment, but if you have a known history.

DR. FOWLER: I wouldn't see any other reason to exclude them unless it is known to be allergic to latex or rubber, which was already discussed.

Then there was a question about the patch size, some debate about whether a one inch by one inch patch or a two centimeter squared patch is necessary. Any thoughts or comments from the panel?

DR. SIMMONS: I think Dr. Hylek had a question.

DR. HYLEK: I believe one of the speakers, Dr. Perrella, had mentioned that the one inch patch isn't even on the market or isn't usable. Is that true and would that be a large cost to come up with this one inch by one inch? Perhaps we could get more information on the existence of that modality.

DR. SIMMONS: I think that is a question for the FDA because it seems that, obviously, if it is not on the market, that we can't use it.

DR. TOMAZIC-JEZIC: Those are not commercial tests for this particular thing because they are testing product. That means actually you are using a particular product. You are cutting out the size, whichever is recommended. I did speak with a number of testing labs and that is what they said they are doing. They take the test article and they cut out the size that is recommended.

DR. HYLEK: Is that because you want to eliminate a non-specific reaction to the actual material that the chemicals are going to be placed upon, the one inch by one inch or is this --

DR. TOMAZIC-JEZIC: The patch is the article per se. The only thing that is put on the top is the occlusion tape that is holding the article in the spot. So, there is no commercial testing tray as dermatologists are usually using.

DR. SIMMONS: I guess the question is why the one by one inch --

DR. HYLEK: As opposed to the two by two centimeter.

DR. TOMAZIC-JEZIC: Well, the reason is that actually in the past we used always one to one for the Draize test for hypoallergenic and I know there was

discussion between dose and the surface by other people, but we based this on our experience before. And as I think somebody reported today, even with those hypoallergenic gloves, which had the one by one inch square size, there were still reports on adverse reactions to hypoallergenic gloves that we received at FDA. I think Dr. Lin mentioned that.

DR. LIN: As I mentioned in the morning in my presentation, this incident in 1989, when the agency allow for hypoallergenic level, that test data, we have seen probably more than a hundred test report and most of the report we have seen is one inch by one inch. I don't know, for some reason, historical, but on the other hand, we have also seen some test report using the two centimeter by two centimeter, but this is very, very small number as compared to most of the report we have seen. It is mostly conducted with one inch by one inch.

DR. SIMMONS: Any other panel members?

DR. WHITEHOUSE: The only comment I would have on that, Madame Chairman, is that it sounded to me like, one, the two by two centimeter patch is more commonly used, let's say, in clinical practice. Two, the one by one, where they use the entire -- are using the entire patch, the ideal is

to sort of equate the dosage so that you have a more equivalent dosage, I think, Dr. Lin, it was in the draft. But also I think I heard that there was -- that maybe some of the reactivity to the allergen might relate also to the concentration locally, so that while you are increasing the square centimeter of the -- by using 2.5 rather than 2.0, you might deliver a greater dose, but you might also not deliver a greater concentration.

So, it strikes me that maybe the two by two approach would be reasonable, two by two centimeter approach would be reasonable, inasmuch as that it is more orthodox, if I may use that term, relative to how things are tested. Maybe Dr. Fowler can help us with that point.

DR. FOWLER: Well, as I think has pointed out, this sort of testing is a little different than a lot of other things that are tested on patches. In this case, the piece of material is the object being tested, obviously, and it is inherently occlusive, the glove piece.

So, you really don't need some sort of other occlusion over that. You just need something to adhere it to the skin. So, I am not sure that I see where the size would make that much difference in cost technically. It may make some difference in reactivity and, again, this --

anecdotally, I can tell you that in individuals, who are suspected of being allergic to a clothing allergen, for instance, a formaldehyde chemical and clothing or a dye, it has been found useful to use larger patches of pieces of clothing for testing, rather than to use -- our standard size for clinical use testing is actually a .8 centimeter circle for patch testing.

So, we tend to use a larger piece and one inch has probably been picked empirically for that. That seems to give a better chance of a reactivity. So, that may be part of where this size question has come from.

DR. WHITEHOUSE: That would mean that there would be less false --

DR. FOWLER: Correct.

DR. SIMMONS: Any of the other panel members have any questions about the size?

[There was no response.]

DR. FOWLER: Moving on, let's move on possibly a couple of slides down the line there about test location. There was a question whether two sites or more or less would need to be done, two geographically different locations for testing to be carried out. Any comments on those items?

DR. HYLEK: Could you just clarify that the

rationale behind the testing in two different geographic locations was really an attempt to control for confounding, that may be introduced by humidity and temperature differences in different areas of the --

DR. TOMAZIC-JEZIC: There are some literature data that indicate that, you know, dry climate would induce such different condition in the skin; also, the different temperature and actually people who were testing in a different seasons in the same environment found these differences.

I don't know how significant those differences are, but that was also a recommendation of those who are doing routine testing that may be beneficial to have at two locations -- I mean, either two locations or two different time of the year or whatever.

DR. WHITEHOUSE: I was just wondering how one would interpret data where you might have positive in one area and negative in another area and what are the two areas that you would contemplate being most likely; upper back and one other?

DR. FOWLER: Now, you are talking body location, not geographic location. This has to do with geographic --

DR. WHITEHOUSE: My apologies.

DR. FOWLER: -- location around the world.

One other comment on the questions about the second claim would be that it may be easier for a company to obtain test subjects, the 25 sensitized test subjects, if they had two or more locations to work from and they could have the work done more rapidly.

Any other comments on that?

[There was no response.]

There are a couple of questions or comments or thoughts about scoring criteria. I will say that dermatologists do use standardized methods for scoring skin reactions on clinical patch testing, but I think some of the thoughts in this document do need to be looked at because the critical thing, as Dr. Maibach indicated, is not so much what the number is, but what that number represents.

I will say also that the ASTM document 77-97 uses a different scoring system than is used clinically for what we would score, for instance, the Phase 2 subjects. So, there has to be some clarification, I think, as this is looked at to realize that as it stands now, what is a 1 plus in the ASTM document is not the same as what we call a 1 plus in a clinical patch test setting. And that has to be resolved, I think, in this.

DR. HYLEK: I just wanted to raise a point of information and help me again in deciphering some of this, but it states in the guidance document that we were given to read before, that symptoms of irritation in Type IV allergy may frequently be indistinguishable. The only positive identification of the two reactions may be the time of the appearance and for delayed hypersensitivity, I would think it would be on the order of 72 hours or somewhere in there.

DR. FOWLER: In individuals, say the Phase 2 group, who are already sensitized, we put much more weight on the late reading than the earlier reading. So, as you will see, the document suggests two readings, once when the patches are removed at 48 hours and then, again, at some later time, two to four days later.

Generally, that late reading is much more relevant than the first one because some of these allergens actually may be mild irritants and that irritation -- this is not universal, but the irritation tends to fade. The allergy reaction actually tends to accelerate.

DR. HYLEK: So, that worrisome false positive that we heard about with the occlusive patch that was only impregnated with water, that would be equivalent to sweating and that would be something that you should really see at

the time you had removed the patch immediately. Wouldn't it be a more --

DR. FOWLER: Essentially, that is right.

DR. HYLEK: Okay. So, that would be important to clarify, when we would be scoring these reactions on what hour, post -- okay.

DR. FOWLER: Yes.

Let's go on and I think some of the -- to finish up with this -- the labeling claims --

DR. LIN: Dr. Fowler --

DR. FOWLER: Yes.

DR. LIN: -- before you leave this subject, I can ask questions and I think the reason that we bring this discussion point up for discussion essentially is that the problem we see this -- as you already indicated earlier, a few minutes ago, most of what dermatologists, when they conducting testing or scoring, usually they don't have a fixed criterion. So, depending on your experience, your perception or -- so, sometimes we see that, you know, somebody may be score 1 plus, but to some dermatologist would say, well, this is very mild redness. Maybe it is not considered erythema.

So, in that situation, very difficult for us --

that would depend on which testing lab. Some dermatologists has very sharp eye. Sometimes some dermatologists probably has a low threshold. Even some redness, they call it .5 or not to mention it. So, in that situation, it is very difficult for our reviewer to judge which would be considered positive or always it is not positive. That is the reason we thought, well, maybe if we can standardize, you know, the scoring criteria and give it some definition when you see what situation that will be considered -- what is your opinion in that regard?

DR. FOWLER: No, I realize that is a problem for you and I agree it has to be standardized before this document is finalized and I think that is something that, you know, probably would be -- you know, can be done with some further discussion. But, I agree. I know that is a problem and that is very critical.

DR. SIMMONS: Well, we cannot determine the standardization today, but are we saying that we want to recommend that you have another meeting to kind of look at scoring specifically?

DR. LIN: Well, that is the reason we sort of decided to use ASTM's scoring system, but in your opinion of symptomatology, is this a scoring system -- is it acceptable

to all the dermatologists in practice?

DR. FOWLER: I certainly can't speak for all dermatologists, but for Dr. Maibach and myself. No, I would have to -- I really have to look at those criteria closely again. I don't have enough total understanding of them right this second to give you an answer. I will be glad to do that and give you an answer later.

Shall we go on to the labeling claims? Let's move on the labeling claims. That is two or three slides down the line if you wish to put them up.

There has been some discussion about different wording for these claims. Comments from the panel members?

Claim 1, regarding potential for inducing sensitization in unsensitized individuals. And, again, I don't think that this -- that we are going to rewrite this right here, but I guess if there are any comments, they should be brought out.

DR. SIMMONS: I think probably both of them. It was clear to me that we probably need to be a little bit more clear.

DR. HYLEK: It seemed to me that several of the speakers were in favor of a much more specific language, actually putting in there the three different chemical

names. And I am just wondering -- I am not sure patients in my practice are that savvy to know what their specific -- what chemical their reaction is to. But on the other hand, someone with a very severe latex allergy that is putting up obstacles for them to continue in their line of work, like the dentist that we heard of this morning, probably would have already sought out a specialist's opinion and would have found out the actual -- I am just curious. In your practice, do most of your -- although you are an allergist, though, but I am curious if the --

DR. FOWLER: No, I am a dermatologist.

DR. HYLEK: I am just not sure that my patients in a general population of Boston would be able to tell me -- and this would be for that sensitized population, who would know. This clearly would not apply to the individuals who haven't a clue if they are going to react to the gloves. But even among the individuals who are sensitized -- this was the first time I heard of these three different chemicals and I have a fairly busy general practice, but I hadn't known myself. So, I am just curious if people would know the language.

MS. CHANDLER: I would like to comment on that. As a consumer rep, I would be remiss if I didn't talk about

all the people who phoned me, faxed me after I surfed the 'Net. I was even invited into the "Rubber Room" to chat.

But there were several people who called with Type I, as well as Type IV, allergy experiences, one of which that just stuck out in my mind was a housewife who found herself allergic to Playtex cleaning gloves initially when she was married. And then a year later delivered -- had a C-section and when they were catheterizing her, had an anaphylactic reaction.

She knew the chemicals she was allergic to because after that she was seen by a dermatologist, had full allergen testing. She and two other individuals, also in the health care industry, who experienced anaphylactic reactions, also knew the chemicals they were allergic to, but others that said, oh, yeah, when I have used latex gloves while providing patient care or whatever, they didn't know anything about the chemicals they were allergic to nor had they gone to a dermatologist or had any allergy testing.

They just assumed on their own when I put on these gloves, I have this allergy. So, therefore, I won't use them anymore. And just talking with other people in their work setting, three comments that consumers made when they called me, that they really wanted to impress upon the

committee and the FDA was the fact that they would love to one day see the powder in gloves treated as second hand smoke because the powder in gloves can be ersalized(?) for 12 hours and can also cause problems.

They do want clear labeling, nothing that really goes into chemicals per se in the real technical sense, but just the fact that this product can be hazardous to your health if you already have an allergy and to remove from all labeling hypoallergenic, the word "hypoallergenic" because it doesn't really anything today.

Also, they wanted to see more hospitals providing latex reenvironments. And I believe someone here from Emory, Dr. Sullivan, was it, that spoke about latex reenvironment, and it is doable. This is definitely an epidemic. I do 30 pelvic exams everyday and I myself have the allergy to the chemicals. So, I use powder-free gloves. That helps that, but my patients are complaining of latex allergies to condoms

So, I mean it is -- we are talking about gloves today, but --

DR. SIMMONS: Did we get a feeling that we wanted to -- a more specific label? I am hearing that we did.

DR. FOWLER: I would think that for the Phase 2 or

the claim 2, the individual chemical names actually are useful for a number of people, who have been tested and know that they are allergic to those chemicals. I mean, it is a very small minority of the general population, but it is very critical to those few people. It is a hundred percent important to those 1 percent of the people or whatever they are.

So, for that, the names probably will mean something. To the general claim 1, it probably would not.

DR. SIMMONS: Let me just kind of summarize, if I can, what I just heard. Just by way of recommendation -- and you can tell me if you are not in agreement or just kind of nod your head, but by way of helping the FDA, it seems that if we look at the sample size, we agree with the sample size and we don't think there should be any change with that, 300 and 25.

If we go on, should the FDA consider excluding individuals with other forms of contact dermatitis, and I think what I heard is unless the person really had a previous history of contact dermatitis, the recommendation is good as it stands. Is that agreeable?

The third, we agree that there should be some clarification about the -- I am missing scoring -- document

size is okay, the document size as it is --

DR. FOWLER: Patch size.

DR. SIMMONS: The patch size is okay. Did I hear that?

And there should be some clarification of scoring. We cannot answer that today. Maybe it would help with Dr. Fowler and some of our other dermatologists to get back with the FDA. I mean, there should be some clarification that we cannot just accept what is here.

The labeling claims, what I am hearing is that particularly proposed claim 2, that we need to have a little bit more specificity as to how we label, whether it is chemicals or more specific information so that the person who has no idea if they are sensitive to an allergen would be a little bit cautious in using the product.

I think they really want the --

[Multiple discussions.]

I kind of skipped the first claim. Oh, that is it, claim 2. That is it. That is where we are.

What we are saying is that where we have name of chemical sensitizer, we just put in the three chemicals? Is that -- would that labeling claim be okay? Are we agreed on that?

DR. WHITEHOUSE: All three chemicals?

DR. FOWLER: I would think also just from a -- this makes sense, that if an individual glove is not manufactured with a particular chemical, then by definition it has to be a reduced sensitizer or reduced potential to cause allergies. So, as one of the speakers before mentioned, that, you know, it would not seem to me to make any sense to withhold the -- or make them go through testing for a chemical that is not in that glove, if, indeed, it is truly not in that glove.

But for the others, that doesn't negate what we said. That is just an additional comment.

DR. HYLEK: Just as a point of ignorance because i don't really know how the FDA does it labeling, is there any reason to put on here any type of an informational statement about this does not include the protein?

DR. SIMMONS: That could be a recommendation. Do you want to make that recommendation and we can add it to our recommendations today?

DR. HYLEK: I would make that recommendation.

DR. SIMMONS: We can make that recommendation that -- are we talking about claim 1 and claim 2?

DR. HYLEK: Well, I think for the consumer, that

they would want to know if they had had a bronchospastic reaction, as Dr. Slater had talked about earlier today, or, God forbid, one of the 11 deaths out of the billion gloves that were used in one year, although that is very rare. But you would not want to mislead people into thinking that, oh, well, this sounds great. I can probably just, you know, put my hands in these for the next 48 hours and not have any --

DR. SIMMONS: So, maybe a statement like that with both labels.

DR. FOWLER: With both claims, there must be an indication that latex Type I allergy is not considered in these hypoallergenic claims.

DR. SIMMONS: I think that would be good. So, we make a recommendation that you add that disclaimer to both.

As far as claim 1, claim 1 is okay with the addition of that disclaimer. Is that agreeable?

DR. LIN: Dr. Simmons, can I also ask -- this is sacred to our heart. The reason that we bring this statement up for discussion, they indicated some -- indicated this statement too long. How many people really can read it and read every word to figure out exactly what this means. So, somebody suggests if there is any way that we can shorten this statement, if, for example, we have this

hypoallergenicity or hypoallergen, ten people see it and right away they can see that the product right away, say, oh, this relieves allergen type of wording.

But here this is kind of too long and that is what the criticism that we have received. Probably at the same time, we also received from our manufacturer, they also say that this is too long. You also have mentioned about protein content also. So, you have go so many statement there and, you know, for health care providers, such as you, do you really have a chance to read this statement and, second, that it would make sense to you and you can really figure out what this product is all about. That is the issue we would like you to provide us with some input to see whether you can make this statement much clearer to the end user when they are in a busy lab, they can look at the box and then really maybe they can see what is the product that they are dealing with.

Thank you.

DR. SIMMONS: Okay. Panel members?

DR. HYLEK: Well, I think that it would -- I am sure in my busy practice that once this became the market standard that I would read it probably through once and then, hopefully, recognize it on the subsequent gloves that

would be placed in my gurney there or my table.

So, I would argue that even though it does seem to be a little verbose, I mean, each word in there is important and I would think that we should keep that. Individuals who are so interested in this issue, which is why we are all here, the length of time it took me to read that first one was probably about five seconds.

DR. SIMMONS: You know, under the caution statement, you can add -- instead of us adding another statement about protein, we can probably put protein in that and make that one sentence. You see where it says "Caution"? So, we can kind of add that. I think everything else is appropriate.

Any other panel member discussion? How can we shorten this?

DR. WHITEHOUSE: Well, Dr. Lin, you know that a camel is a horse made by a committee. Somebody has to sit down, perhaps the chair of this committee, with you and come out and reduce the words down to the very minimum, but not to the point of od(?) absurden(?). My only concern would be in the second claim and adding the chemical sensitizers that you end up using some of these organic chemicals, comma, comma, comma, that people will not be aware of those. But

on the other hand, they may well be through their primary care providers if they know, just like some people know that they are allergic to sesame seeds or to -- so that I think that a little bit of wordiness may be a safety factor for the person involved.

DR. LIN: Just one more point. I think in Dr. Perrella's presentation, he also suggests that uses, training, uses, instruction would help if -- you know, to teach health skill worker what is going on in the glove or latex medical product, what the manufacturing process --

DR. EDMISTON: Actually, that is going on. In my hospital and every hospital, we have latex committees. So, I can tell you from the operating room perspective, the nurses in the operating room are scanning every single product that is introduced into that environment and scheduling cases such that they don't conflict with the use of any latex.

So, I can tell you our institution is well aware of it and I suspect the message is getting out. So, I am not sure any additional educational efforts are needed, at least from this committee.

DR. SIMMONS: Have the FDA come out with an educational -- maybe there could be an educational video

sent out to the hospitals that may be produced with industry. We can make that recommendation.

PARTICIPANT: FDA is working with NIOSH. In fact, there was a meeting just this afternoon to talk about a teleconference that would be down linked to hospital sites and perhaps even including continuing medical education credits and things like that, to discuss the whole -- a whole raft of issues and that includes the protein, the Type I reaction, the powder and certainly the idea of trying to explain the difference between the Type IV reactions to chemical and Type I reactions to protein, I would think, could be worked into this.

I know that the AMA and the American Nursing Association is being contacted also to be involved in this. So, yes, I think education is a viable alternative.

DR. SIMMONS: May I ask the panel if anyone else has any comments, any panel members?

[There was no response.]

May I ask the FDA, have we answered your questions sufficiently this afternoon?

DR. LIN: We appreciate your input and your input is very, very useful to us and we really appreciate.

DR. SIMMONS: We are finished.

I will now like to adjourn this meeting and also announce we will not have a meeting tomorrow.

Thank you for coming.

[Whereupon, at 4:45 p.m., the meeting was concluded.]